DIOXOLANE DERIVATIVES AS CELL ADHESION INHIBITORS

Field of the Invention

The present invention relates to dioxolane derivatives as cell adhesion inhibitors. These compounds can be useful for inhibition and prevention of cell adhesion and cell adhesion-mediated pathologies, including inflammatory and autoimmune diseases such as bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, allograft rejection or psoriasis. This invention also relates to pharmacological compositions containing the compounds of the present invention, and the methods of treating bronchial asthma, rheumatoid arthritis, multiple sclerosis, type I diabetes, psoriasis, allograft rejection, and other inflammatory and/or autoimmune disorders, using the compounds.

Background of the Invention

Cell adhesion is a process by which cells associate with each other, migrate towards a specific target or localize within the extra-cellular matrix. These interactions are mediated by specialized molecules called cell adhesion molecules (CAMs). CAMs have been demonstrated to participate in various cell-cell, cell-extracellular matrix, and platelet-platelet interactions. They influence the adhesion of leukocytes to the vascular endothelium, their transendothelial migration, retention at extravascular sites and activation of T cells and eosinophils. These processes are central to the pathogenesis of inflammatory and autoimmune diseases. Therefore, CAMs are considered as potential targets to treat such disorders.

CAMs can be classified into three groups - integrins, selectins and the immunoglobulin superfamily. Of these, integrins are key mediators in the adhesive interactions between hemopoietic cells and their microenvironment. They are comprised of alpha-beta heterodimers that integrate signals from outside to the inside of cells and vice versa. Integrins can be classified on the basis of the beta subunits they contain. For example, the beta-1 subfamily contains beta-1 subunit noncovalently linked to one of the 10 different alpha subunits.

The alpha-4 beta-1 integrin, also known as VLA-4 (very late activation antigen 4), is a member of the beta-1 integrin family, and comprises alpha-4 and beta-1 subunits. It interacts with two specific ligands, the vascular cell adhesion molecule (VCAM-1) and the CS1 region of the protein fibronectin. Adhesion mediated by VLA-4 is central to the process of transendothelial migration of leukocytes. Ligation of VLA-4 is followed by

gross rearrangement of the cytoskeleton, leading to flattening of cells along the blood vessel wall, followed by expression of specific molecules, which digest the endothelial cell wall and diapedesis. Once in the extraluminal region, the interactions of VLA-4 with extracellular fibronectin play a crucial role in migration to the site of inflammation, T cell proliferation, and the expression of cytokines and inflammatory mediators. In addition, VLA-4 ligation provides co-stimulatory signals to the leukocytes, resulting in enhanced immunoreactivity. Therefore, it is expected that VLA-4 antagonists would ameliorate the immune response through twofold actions: inhibition of T cell recruitment at the site of inflammation; and inhibition of costimulatory activation of immune cells.

In support of this concept, inhibitors of VLA-4 interactions have demonstrated beneficial therapeutic effects in several animal models of inflammatory, and allergic diseases including sheep allergic asthma.

The region of CS1 moiety of fibronectin involved in the interaction with VLA-4 has been identified as the tripeptide Leu-Asp-Val, also known as LDV. Taking a lead from this, several peptides containing the LDV sequence were synthesised which have shown to inhibit the *in vivo* interaction of VLA-4 to its ligands.

Despite these advances, there remains a need for small and specific inhibitors of VLA-4 dependent cell adhesion molecules. Engineering of new generation of more stable and potent molecules with improved oral efficacy would provide useful agents for treatment, prevention or suppression of various inflammatory pathologies mediated by VLA-4 binding.

U.S. Patent No. 6,329,344 B1 discloses several monosaccharide derivatives as cell adhesion inhibitors. It generally relates to substituted pentose and hexose monosaccharide derivatives, which exhibit potent anti-cell adhesion and anti-inflammatory activities. PCT application WO 00/42054 discloses several monosaccharide derivatives as cell adhesion inhibitors.

Patent application WO 00/43369 provides compounds which bind to VLA-4, as well as triazine derivatives which inhibit leukocyte adhesion mediated by VLA-4. WO 99/06434 discloses 4-aminophenylalanine type compounds which inhibit leukocyte adhesion mediated by VLA-4. WO 01/12186 discloses cell adhesion inhibitors which interact with VLA-4 molecules and inhibits VLA-4 dependent cell adhesion. WO 98/58902 discloses molecules which are potent inhibitors of $\alpha_4\beta_1$-mediated adhesion to

either VCAM or CS-1 and which can be used for treating or preventing $\alpha_4\beta_1$-mediated adhesion mediated conditions.

Ann. Rep. Med. Chem. 37, (2002) summaries the highlights of work in the area of VLA-4 biology and small molecule antagonists. U.S. Patent No. 6,291,511 discloses several biarylalkanoic acids as cell adhesion inhibitors.

GB 2354440 discloses several aryl amides as cell adhesion inhibitors. WO 98/53814 discloses heterocyclic amide compounds as cell adhesion inhibitors. WO 01/12183 discloses heterocyclic amides as cell adhesion inhibitors. WO 99/20272 and U.S. Patent No. 6,069,163 discloses several azapeptide acids as cell adhesion inhibitors. U.S. Patent 6,020,347 discloses 4-substituted-4-piperidine carboxamide derivatives useful in the inhibition or prevention of cell adhesion and cell adhesion mediated pathologies. U.S. Patent 6,191,171 discloses para-aminomethyl aryl carboxamide derivatives as cell adhesion inhibitors. U.S. Patent 6,090,841 discloses substituted pyrrole derivatives as cell adhesion inhibitors. *Bioorg & Med. Chem.*, 10 (2002), 1567-1580 discloses synthesis of potential thrombin inhibitors and incorporation of tartaric acid templates as P2 proline mimetics.

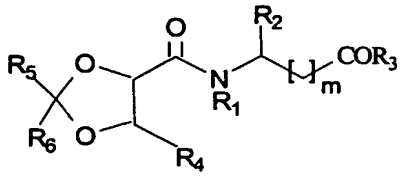
Summary of the Invention

Herein are disclosed classes of compounds containing a dioxolane moiety which may be used as therapy for the inhibition, prevention and suppression of VLA-4 mediated cell adhesion and pathologies associated with such adhesion.

The compounds of the present invention may be screened for inhibitory activity in VLA-4 mediated cell adhesion assay and the classical murine hypersensitivity assay in mice. These compounds could be used in treatment of chronic, cell adhesion mediated, allergic, autoimmune and inflammatory disorders, such as bronchial asthma, multiple sclerosis, rheumatoid arthritis etc. Some of the prior art describes development of peptide derivatives as cell adhesion antagonists for treatment of these diseases. However, because treatment of chronic diseases requires prolonged (mid term to long term) administration of drugs, development of small molecule, specific, orally available inhibitors of cell adhesion would be very beneficial.

Herein are provided substituted dioxolane derivatives, which can be used as cell adhesion inhibitors.

In accordance with one aspect of the invention, there is provided a compound having the structure of Formula I



Formula I

its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides

wherein

m is an integer from 0-2;

$\mathbf{R_1}$ can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroarylalkyl, or heterocyclylalkyl;

$\mathbf{R_2}$ can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl;

$\mathbf{R_1}$ and $\mathbf{R_2}$ may together join to form a cyclic ring (3-8 membered), which may be optionally benzofused, containing 0-4 heteroatoms such as O, S, or N, wherein the rings may be substituted with one or more of alkyl, alkenyl, alkynyl, amino, substituted amino, cycloalkyl, carboxy, alkoxy, aryloxy, halogen (F,Cl, Br, I), aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl;

$\mathbf{R_3}$ can be NH_2, NHOH, NHOR (wherein R can be alkyl, alkenyl, alkynyl, cycloalkyl or aralkyl), or OR_m (wherein R_m can be hydrogen, alkyl, aralkyl, aryl, or metal ions (Na^+, K^+, Li^+, Ca^+ or Mg^+));

$\mathbf{R_4}$ can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, $-(CH_2)_{1-4}$-O-R' (wherein R' can be selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, aryl, heterocyclylalkyl, or heteroarylalkyl), $-C(=O)-R_3$ (wherein R_3 is the same as defined above) $-C(=O)R_Z$ (wherein R_z is $-NR_7R_8$ wherein R_7 and R_8 can be independently selected from hydrogen (provided that both R_7 and R_8 are not hydrogen, represented as "amino"), alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, hydroxyalkyl, aralkyloxy, aryl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, SO_2R_9 (wherein R_9 can be selected from alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl); or $\mathbf{R_7}$ and $\mathbf{R_8}$ may together join to form a cyclic ring (3-8 membered),

which may be optionally benzofused, containing 0-4 heteroatoms such as O, S, or N, wherein the rings may be substituted with one or more of alkyl, alkenyl, alkynyl, amino, substituted amino, cycloalkyl, carboxy, alkoxy, hydroxy, oxo, aryloxy, aryl, halogen (F,Cl, Br, I), aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl; or

$(CH_2)_{1-4}NR_xR_y$ [wherein R_x and R_y can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, $-YR_u$ (wherein Y is C(=O), C(=S) or SO_2 and R_u is alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl), $-C(=T)NR_u$ (wherein T is oxygen, sulphur, $-CH(NO_2)$, $-N(NO_2)$ or -N(CN) and R_u is the same as defined above) or $-C(=O)OR_u$ (wherein R_u is the same as defined above)].

R_5 and **R_6** may be independently selected from hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aryl, or aralkyl; or **R_5** and **R_6** may together join to form a cycloalkyl ring.

The following definitions apply to terms as used herein.

The term "alkyl" unless and otherwise specified refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms.

Alkyl groups may further be substituted with one or more substituents selected such as alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, aryl, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryloxy, aminosulfonyl, aminocarbonylamino, aminothiocarbonylamino, hydroxyamino, alkoxyamino, nitro, SH, S-alkyl, S-Salkyl, –SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl, further alkyl may be substituted with a group represented by $(CH_2)_{0-3}C(=O)NR_7R_8$ wherein R_7 and R_8 are same as defined earlier.

Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxy-alkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_{12}$, where R_{12} can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl and heterocyclyl and n is 0, 1 or 2; or

or an alkyl group as defined above that is interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and $-NR_a-$, where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3,

amino, substituted amino, cyano, and $-S(O)_nR_{12}$, where n and R_{12} are the same as defined earlier;

or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with cis or trans geometry either in a acyclic or cyclic ring system wherein the cyclic may include mono- or multicyclic ring forms. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom.

Alkenyl groups may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl, further alkenyl may be substituted with a group represented by $(CH_2)_{0-3}C(=O)NR_7R_8$ wherein R_7 and R_8 are the same as defined earlier. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_{12}$, where R_{12} is the same as defined above and n is 0, 1 or 2.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms. In the event that alkynyl is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom.

Alkynyl groups may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, SO_2-aryl and $-SO_2$-heteroaryl; further alkynyl may be substituted with a group represented by $(CH_2)_{0-3}C(=O)NR_7R_8$ wherein R_7 and R_8 are the same as defined earlier. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_{12}$, where R_{12} is the same as defined above and n is 0, 1 or 2.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, for example cyclobutyl, cyclopentyl, adamantyl and the like.

Cycloalkyl groups may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, amino, aminocarbonyl, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl; further cycloalkyl may be substituted with a group represented by $(CH_2)_{0-3}C(=O)NR_7R_8$ wherein R_7 and R_8 are the same as defined earlier. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_{12}$, where R_{12} is the same as defined above and n is 0, 1 or 2.

"Alkoxy" denotes the group O-alkyl wherein alkyl is the same as defined above.

"Aralkyl" refers to $(CH_2)_p$ aryl, wherein p is an integer in the range of 1-6 and aryl is as defined below.

The term "aryl" herein refers to phenyl or naphthyl ring and the like, which may optionally be fused to cycloalkyl or heterocyclyl. The aryl group may optionally be substituted with 1 to 3 substituents such as aryloxy, cyano, amino, aminothiocarbonyl, alkoxycarbonyl, azido, oxo, thiocarbonyl, thiol, cycloalkoxy, aminosulfonyl, aminocarbonylamino, hydroxy, hydrogen, halogen (F, Cl, Br, I), alkyl, alkenyl, alkynyl, cycloalkyl, $(CH_2)_{0-3}C(=O)NR_7R_8$ wherein R_7 and R_8 are the same as defined earlier, -$NHC(=O)R_9$ (wherein R_9 is selected from hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl), alkoxy, alkenyloxy, alkynyloxy, carboxy, nitro, aryl, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl, heteroaryl, heterocyclyl, amino, NR_7R_8 wherein R_7 and R_8 are the same as defined above; $-O-(CH_2)_{0-4}-(C=O)_{0-1}R_9$ or $-NH-O-(CH_2)_{0-4}-(C=O)_{0-1}R_9$ wherein R_9 is the same as defined above; SO_nR_{12} wherein n is an integer in the range of 0-2 and R_{12} is the same as defined above; $C(=O)R'$ wherein R' can be hydrogen, alkyl, aryl, aralkyl, hydroxy, alkoxy, amino or substituted amino.

The term "carboxy" as defined herein refers to $-C(=O)O-R_{10}$ wherein R_{10} can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl.

"Aryloxy" denotes the group O-Aryl wherein aryl is the same as defined above.

"Aralkoxy" denotes the group O-aralkyl wherein aralkyl is the same as defined above.

"Substituted amino" unless and otherwise specified refers to a group $-N(R_r)_2$ wherein each R_r can be hydrogen (provided that both R_r groups are not hydrogen), alkyl, alkenyl, alkynyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, SO_2R_{12} wherein R_{12} is the same as defined above; $C(=O)R_{12}$ wherein R_{12} is the same as defined above; $C(=O)OR^t$ wherein R^t can be alkyl, aralkyl, heteroarylalkyl, aryl, heteroaryl or heterocyclyl. Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, carboxyalkyl, aminocarbonyl, hydroxy, alkoxy, halogen, CF_3, amino, substituted amino, cyano, and $-S(O)_nR_{12}$, where R_{12} is the same as defined above and n is 0, 1 or 2.

The term "heteroaryl" as used herein refers to an aromatic ring structure containing 5 or 6 carbon atoms, or a bicyclic aromatic group having 8 to 10 carbon atoms, with one or more heteroatom(s) such as N, O and S optionally substituted with 1 to 3 substituent(s) which can be halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkoxy, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl, aralkyl, cyano, nitro, amino or substituted amino, cyano, oxo, carboxy; $C(=O)R'$ wherein R' is the same as defined earlier; $C(=O)NR_7R_8$ wherein R_7 and R_8 are the same as defined earlier; or SO_nR_{12} wherein n and R_{12} are the same as defined earlier. Further, heterocryl groups may optionally be fused to an aryl ring wherein aryl is the same as defined earlier.

The term 'heterocyclyl" as used herein refers to a non aromatic cycloalkyl group having 5 to 10 atoms in which 1 to 3 carbon atoms in a ring are replaced by heteroatoms such as O, S or N, and are optionally benzofused or fused heteroaryl of 5-6 ring members and/or are optionally substituted wherein the substituents can be halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl, aryl, alkoxy, aralkyl, cyano, nitro, amino or substituted amino, cyano, oxo; $=O)R'$ wherein R' is the same as defined earlier; $C(=O)NR_7R_8$ wherein R_7 and R_8 are the same as defined earlier; or SO_nR_{12} wherein n and R_{12} are the same as defined earlier.

The term "Heteroarylalkyl" refers to heteroaryl (wherein heteroaryl is same as defined earlier) linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6.

The term "Heterocyclylalkyl" refers to heterocyclyl (wherein heterocyclyl is same as defined earlier) linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6.

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs or N-oxides of these compounds are also provided.

Pharmaceutical compositions containing the compounds, which may also contain pharmaceutically acceptable carriers or diluents, can be used for the treatment of cell adhesion mediated pathologies including inflammatory and autoimmune diseases such as bronchial asthma, rheumatoid arthritis, type I diabetes, multiple sclerosis, allograft rejection or psoriasis.

The term "leaving group" generally refers to groups that exhibit the desirable properties of being labile under the defined synthetic conditions and also, of being easily separated from synthetic products under defined conditions. Examples of such leaving groups include but are not limited to halogen (F, Cl, Br, I), triflates, tosylate, mesylates, alkoxy, thioalkoxy, hydroxy radicals and the like.

The term "Protecting groups" is used herein to refer to known moieties which have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also, protecting groups, unless otherwise specified, may be used with groups such as hydroxy, amino, carboxy and examples of such groups are found in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Ed, John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting group employed is not critical as long as the derivatised moieties/moiety is/are stable to conditions of subsequent reactions and can be removed at the appropriate point without distrupting the remainder of the molecule.

Compounds provided herein can contain one or more asymmetric carbon atoms and thus can occur as racemates, mixtures of enantiomers, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included herein. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are envisioned as

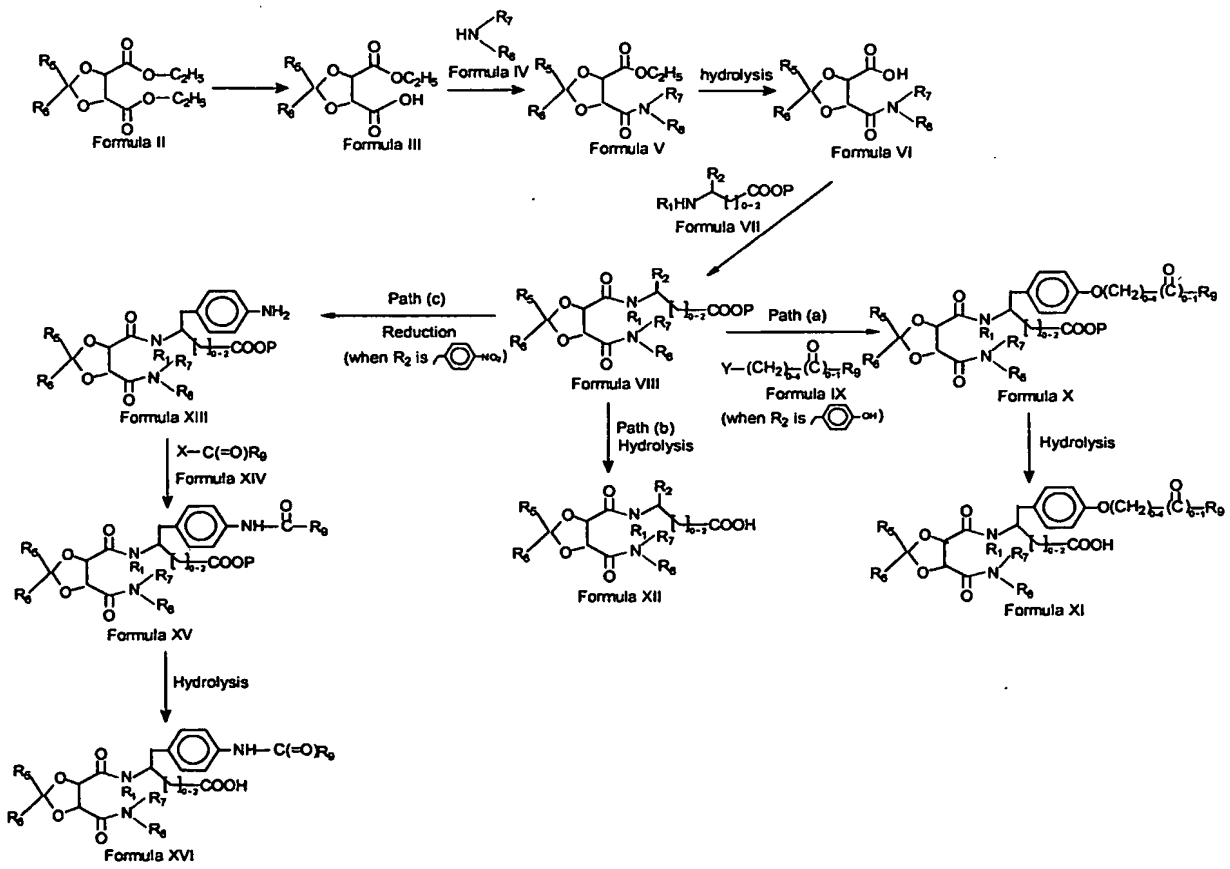
part of the invention. Also, geometric isomers of olefins, C=N double bonds and the like, can be present in the compounds of this invention, and all such stable isomers are contemplated.

Other aspects will be set forth in accompanying description which follows and in the part will be apparent form the description or may be learnt by the practice of the invention.

Detailed Description of the Invention

The compounds disclosed herein may be prepared by techniques well known in the art and familiar to a synthetic organic chemist of ordinary skill. In addition, the compounds provided herein may be prepared by the following reaction sequences as depicted in Schemes I, II, III and IV.

Scheme I



A compound of Formula XI, XII and XVI can be prepared according to Scheme I. Thus, a compound of Formula II is hydrolysed to give a compound of Formula III, which on condensation with a compound of Formula IV gives a compound of Formula V (wherein R_7 and R_8 are the same as defined earlier), which on further hydrolysis gives a compound of Formula VI, which on condensation with a compound of Formula VII (wherein P is a protecting group such as methyl, ethyl, t-butyl or benzyl) gives a compound of Formula VIII (wherein R_2 is the same as defined earlier), which on condensation with a compound of Formula IX (Path a) (wherein Y is Cl, Br, I, O-Ms or O-Ts) gives a compound of Formula X (wherein R_9 is the same as defined earlier), which is finally hydrolyzed to give a compound of Formula XI (Formula I, R_1 = H, R_2 = aralkyl, R_3 = $-OR_m$ where R_m is H, R_4= $-C(=O)R_z$ where R_z is $-NR_7R_8$ and R_5 and R_6 may be independently selected from hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aryl, or aralkyl; or $\mathbf{R_5}$ and $\mathbf{R_6}$ may together join to form a cycloalkyl ring). For path a), $\mathbf{R_2}$ is p-hydroxybenzyl.

The hydrolysis of a compound of Formula II to a compound of Formula III can be carried out in a solvent system, for example tetrahydrofuran, methanol, dioxane, ethanol or water or combinations thereof. The hydrolysis of a compound of Formula II to compound of Formula III can be carried out in the presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. The condensation of a compound of Formula III with compound of Formula IV to give a compound of Formula V can be carried out in an organic solvent, for example tetrahydrofuran, dichloromethane or dimethylformamide. The condensation of a compound of Formula III with a compound of Formula IV can be carried out in the presence of an organic base, for example N-methylmorpholine, diisopropylethylamine or triethylamine. The condensation of a compound of Formula III with a compound of Formula IV can be carried out in a condensing agent, for example 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride, dicyclohexylcarbodiimide or by a mixed anhydride reaction using chloroformates, for example ethyl chloroformate or isobutyl chloroformate. The hydrolysis of a compound of Formula V to give a compound of Formula VI can be carried out in a solvent system, for example tetrahydrofuran, methanol, ethanol, dioxane or water or combinations thereof. The hydrolysis of a compound of Formula V to give a compound of Formula VI can be carried out in the presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. The condensation of a compound of Formula VI with a compound of Formula VII to give a compound of Formula VIII can be carried out in a organic

solvent, for example tetrahydrofuran or dimethylformamide. The condensation of a compound of Formula VI with a compound of Formula VII can be carried out in the presence of a condensing agent, for example 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide or dicyclohexylcarbodiimide. The condensation of a compound of Formula VI with a compound of Formula VII can be carried out in the presence of a base, for example N-methylmorpholine, diisopropylethylamine or triethylamine. The reaction of a compound of Formula VIII (Path a) with a compound Formula IX to give compound of Formula X can be carried out in an organic solvent, for example acetone, dichloromethane, carbon tetrachloride, dimethylformamide or chloroform.

The reaction of a compound of Formula VIII with a compound Formula IX can be carried out in the presence of a base, for example, sodium hydride, sodium carbonate or potassium carbonate. The hydrolysis of a compound of Formula X to give a compound of Formula XI can be carried out in a solvent system, for example ethanol, dimethylformamide, dimethylsulphoxide, dioxane, tetrahydrofuran, methanol or water or combination thereof. The hydrolysis of a compound of Formula X (when P is methyl, ethyl or benzyl) to give a compound of Formula XI can be carried out in the presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. Alternatively, the hydrolysis of a compound of Formula X (when P is tert-butyl) to give a compound of Formula XI can be carried out in the presence of an acid, for example trifluoroacetic acid or hydrochloric acid, in a solvent, for example tetrahydrofuran in water or dichloromethane.

Compound(s) prepared following the procedure described in Scheme1 (Path a) are:

(S)-3-[4-(2,6-difluoro-benzyloxy)phenyl]-2-{[(4R,5R)-5-(2-methoxy-benzyl-carbamoyl)-[1,3]-dioxolane-4-carbonyl]-amino}-propionic acid (Compound no. 6)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-difluoro-benzyloxy)-phenyl]-propionic acid (Compound No. 8)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 9)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-methoxy-benzyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No.10)

Lithium salt of (S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(3-piperidin-1-yl-propoxy)-phenyl]-propionate (Compound No.11)

Lithium salt of (S)-2-{[(4R,5R)-5-(2-Methoxy-benzyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(3-piperidin-1-yl-propoxy)-phenyl]-propionate (Compound No. 12)

Lithium salt of (S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxalane-4-carbonyl]-amino}-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-propionate (Compound No. 13)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-difluoro-benzyloxy)-phenyl]-propionic acid (Compound No. 14)

Morpholine-4-carboxylic acid 4-((S)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-2-carboxy-ethyl)-phenyl ester (Compound No. 15)

4-Methyl-piperazine-1-carboxylic acid 4-((S)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-2-carboxy-ethyl)-phenyl ester (Compound No. 16)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 25)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2-chloro-benzyloxy)-phenyl]-propionic-acid (Compound No. 26)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-prop-2-ynyloxy-phenyl)-propionic-acid (Compound No. 27)

(S)-2-{(4R,5R)-5-(3,5-Dichlorophenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-difluoro-benzyloxy]-phenyl]-propionic-acid (Compound No. 30)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-phenyl-carbamoyl-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (compound no 32)

-(S)-3-[4-2-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(morpholine-4-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino-propionic acid (Compound No.55)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(3,5-dichloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic-acid (Compound No.71)

A compound of Formula XII can be prepared according to Scheme I. Thus, hydrolyzing a compound of Formula VIII (Path b) can give a compound of Formula XII (Formula I, R_1 =H, R_3 = -OR_m where R_m is H, R_4= -C(=O)R_z where R_z = -NR_7R_8 and R_5 and R_6 are the same as defined earlier).

The hydrolysis of compound of Formula VIII (when P is a protecting group such as methyl, ethyl or benzyl) to give a compound of Formula XII can be carried out in the presence of an organic base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. Alternatively, the hydrolysis of a compound of Formula VIII (when

P is tert-butyl) to give a compound of Formula XI can be carried out in the presence of an acid, for example trifluoroacetic acid or hydrochloric acid.

Compounds prepared following the procedures described in Scheme I (Path b) are:

(S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-hydroxy-phenyl)-propionic acid (Compound No. 1)

(S)-3-(4-Hydroxy-phenyl)-2-{[(4R,5R)-5-(2-methoxy-benzyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 4)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-hydroxyl-phenyl)-propionic acid (Compound No. 24)

(S)-3-(4-(2,6-Dichlorobenzyloxy)-phenyl]-2-[{(4R,5R)-5-[thiophen-2-yl-methyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 31)

(S)-2-{[(4S,5S)-5-(2-Chlorophenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[(pyridin-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No 33)

(S)-2-{[(4S,5S)-5-(Chlorophenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichlorobenzloxy-phenyl]-propionic acid (Compound No.34)

Lithium salt of (S)-2-[{(4R,5R)-5-Cyclopropyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichlorobenzyloxy)-phenyl]-propionate (Compound No. 36)

(S)-2-[{(4R,5R)-5-Cyclohexane-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No 37)

(S)-3-[4-(2,6-Dichlorobenzyloxy)-phenyl]-2-{([4R,5R)-5-(thiazol-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 38)

(S)-2-{[(4R,5R)-5-(Cyclopropyl-carbamoyl)-[1,3]dioxolane-4-carbonyl)-amino]-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No 39)

(S)-2-[{(4R,5R)-5-Cyclohexyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 40)

(S)-2-{[4R,5R)-5-(3,5-Dichloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbamoyl]-amino}-3-{4-[(pyridine-4-carbonyl-amino]-phenyl}-propionic acid (Compound No. 41)

(4R,5R)-5-[(S)-1-Carboxy-2-[4-(hydroxy-phenyl)-ethyl-carbamoyl]-[1,3]dioxolane-4-carboxylic acid ethyl ester (Compound No. 42)

(S)-2-{[(4R,5R)-5-(2,6-Dichloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic-acid (Compound No. 45)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-isopropylcarbamoyl-[1,3]dioxolane-4-carbonyl}-amino]- propionic acid (Compound No.47)

(S)-2-{[(4R,5R)-5-(Benzothiazol-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No.53)

(S)-3-[4-(2,6,-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,3-dihydro-indole-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 62)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(5-methyl-[1,3,4]thiadiazol-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No.63)

(S)-2{[(4R,5R)-5-(Biphenyl–2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-hydroxyphenyl)-propionic acid (Compound No. 64)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[4R,5R)-5-(2,6-dichlorophenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 72)

(S)-2-{[4R,5R)-5-(Bis-thiophen-2-ylmethyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 88)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-diethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 90)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-difluoro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 92)

(S)-2-{[(4R,5R)-5-(2,6-Difluoro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl)-amino}-3-(4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 93)

(S)-2-{[(4R,5R)-5-(2,6-Diethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 94)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-2-phenyl-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 98)

(S)-3-[4-(2,6-Dichlorobenzyloxy)-phenyl]-2-{[(4R,5R)-5-(3,4-dimethyl-isoxazol-5-ylcarbamoyl)-[1,3]-dioxolane-4-carbonyl]amino-propionic acid (Compound No. 107)

{2-[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolone-4-carbonyl]-1,2,3,4-tetrahydro-isoqunoline}-3-carboxylic acid (Compound No. 109)

2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(1H-indol-3-yl)-propionic acid (Compound No. 110)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 111)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-2-methyl-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 113)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-2,2-dimethyl-[1,3]dioxolane-4-carbonyl]amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 1-15)

(S)-2-{[(4R,5R)-5-(2-Cyclopentyloxy-5-fluoro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 133)

3-Benzo[1,3]dioxol-5-yl-3-{[(4R,5R)-5-(2-chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 134)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(2-methoxy-biphenyl-4-yl)-propionic acid (Compound No. 135)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-fluoro-phenyl)-propionic acid (Compound No. 136)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(2,6-dimethoxy-biphenyl-4-yl)-propionic acid (Compound No. 137)

(S)-3-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 138)

3-[((4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-(3,4-dimethoxy-benzyl)-amino]-propionic acid (Compound No. 140)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-(3,5-dichloro-pyridin-4-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 142)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-[((4R,5R)-5-(2-fluoro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 143)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-({(4R,5R)-5-[2-(1H-indol-3-yl)-ethylcarbamoyl]-[1,3]dioxolane-4-carbonyl}-amino)-propionic acid (Compound No. 144)

(S)-2-[((4R,5R)-5-Cyclohexylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 145)

(S)-2-[((4R,5R)-5-(Biphenyl-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 147)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-({(4R,5R)-5-[(thiophen-2-ylmethyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino)-propionic acid (Compound No. 148)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(thiazol-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 150)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(piperidin-1-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 154)

A compound of Formula XVI can be prepared according to Scheme I. Thus a compound of Formula VIII (Path c) is reduced to give compound of Formula XIII (wherein R_7 and R_8 are the same as defined earlier), which on condensation with a compound of Formula XIV (wherein X is OH, Cl or Br) gives a compound of Formula XV (wherein R_9 is the same as defined earlier), which is finally hydrolysed to give a compound of Formula XVI (Formula I, R_1 =H, R_2=aralkyl, R_4= -C(=O)R_z where R_z is -NR_7R_8 and R_5 and R_6 are the same as defined earlier). For path c), $\mathbf{R_2}$ is p-nitro benzyl.

The reduction of a compound of Formula VIII to give a compound of Formula XIII can be carried out in the presence of hydrogen using a catalyst, for example palladium on carbon or platinum on carbon. The condensation of a compound of Formula XIII with a compound of Formula XIV to give a compound of Formula XV can be carried out in an organic solvent, for example dimethylformamide, tetrahydrofuran or dimethylsulphoxide. The condensation of a compound of Formula XIII with a compound of Formula XIV can be carried out in the presence of an organic base, for example N-methylmorpholine, triethylamine or diisopropylethylamine. The condensation of a compound of Formula XIII (when X is OH) with a compound of Formula XIV can be carried out in the presence of a condensing agent, for example 1-(3-dimethylaminopropyl)-3-carbodiimide or dicyclohexyl carbodiimide or by a mixed anhydride reaction using chloroformates, for example ethyl chloroformate or isobutyl chloroformate. Alternatively, the condensation of a compound of Formula XIII (when X is Cl or Br) with a compound of Formula XIV can be carried out in the presence of an organic base, for example N-methylmorpholine, triethylamine or diisopropylethylamine. The hydrolysis of a compound of Formula XV to give a compound of Formula XVI can be carried out in a solvent or solvent system, for example ethanol, tetrahydrofuran, dimethylformamide, dimethylsulphoxide, dioxane, methanol or water or combinations thereof. The hydrolysis of a compound of Formula XV (when P is a protecting group such as methyl, ethyl or benzyl) to give a compound of Formula XVI can be carried out in the presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. Alternatively, the hydrolysis of a compound of Formula XV (when P is tert-butyl) to give a compound of Formula XVI can be carried out in the presence of an acid, for example trifluoroacetic acid or hydrochloric acid.

Compound(s) prepared following the procedure described in Scheme 1 (path c) are:

(S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 2)

(S)-3-(4-Benzoylamino-phenyl)-2-{[(4R,5R)-5-(2-chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 3)

(S)-2-{[(4R,5R)-5-(2-Methoxy-benzylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 5)

(S)-3-(4-Benzoylamino-phenyl)-2-{[(4R,5R)-5-(2-methoxy-benzylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 7)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 17)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(2,6-dichloro-pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 18)

(S)-2-{[(4R,5R)-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[(piperidine-4-carbonyl)-amino]-phenyl}-propionic-acid, salt with trifluoroacetic acid (Compound No.19)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[(pyridine-3-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 20)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[(pyridine-2-carbonyl)-amino]-phenyl}-propionic-acid (Compound No. 21)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[6-bromo-pyridine-2-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 22)

(S)-3-(4-Benzoylamino-phenyl)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 23)

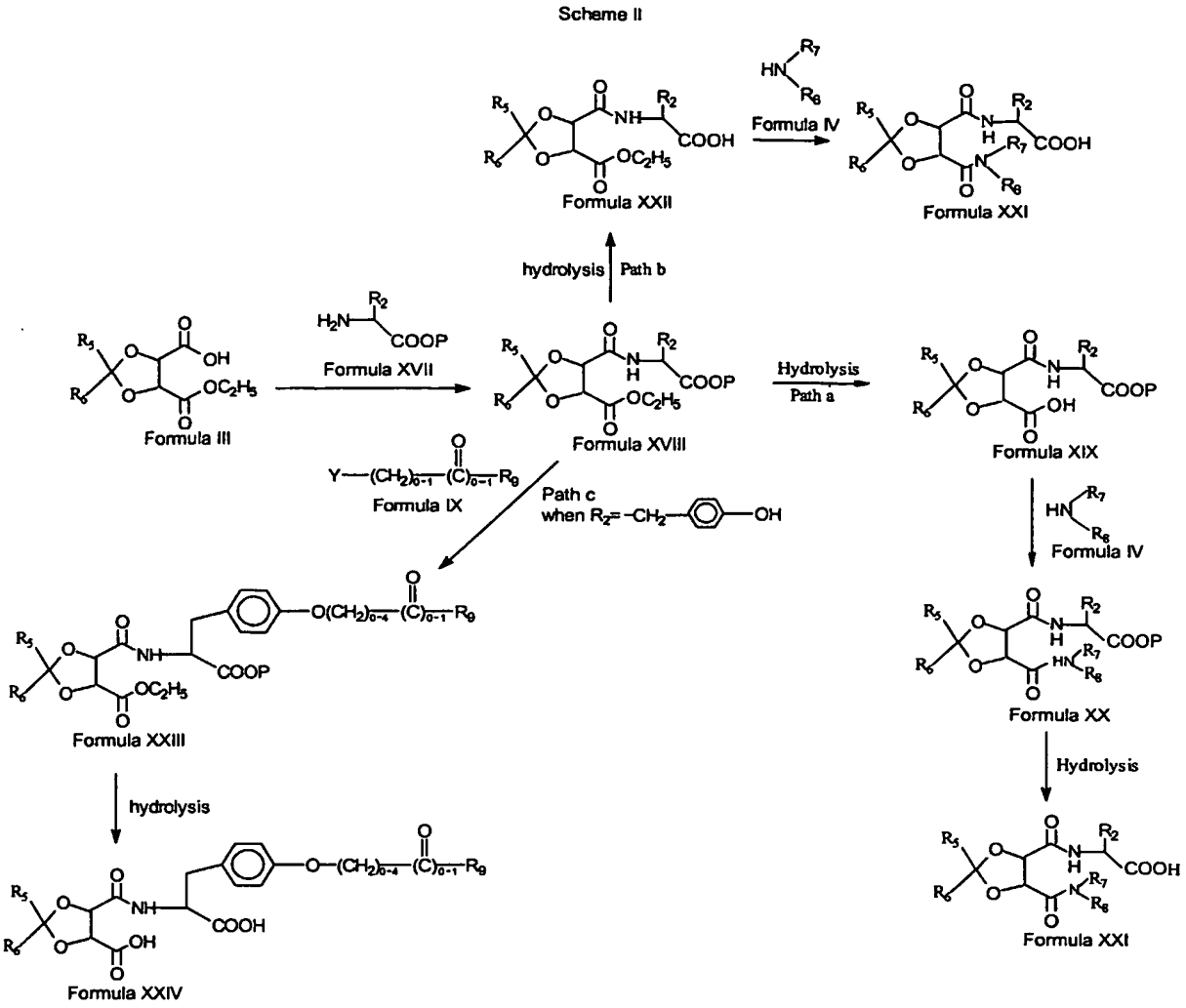
(S)-3-{4-[(2,6-Dichloro-pyridine-4-carbonyl)-amino]-phenyl}-2-{[(4R,5R)-5-(2-methoxy-benzylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 28)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2-methoxy-benzyl-amino)-phenyl]–propionic acid (Compound No 29)

(S)-3-(4-benzoylaminophenyl)-2-[{(4R,5R)-5-(isopropyl-carbamoyl)-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 43)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(2-methoxy-benzylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 151)

Scheme II



A compound of Formula XXI can be prepared according to Scheme II. Thus, a compound of Formula III is condensed with a compound of Formula XVII (wherein P is the same as defined earlier) to give a compound of Formula XVIII (wherein R_2 is the same as defined earlier), which on hydrolysis (Path a) gives a compound of Formula XIX, which on condensation with a compound of Formula IV gives a compound of Formula XX (wherein R_7 and R_8 are same as defined earlier), which is finally hydrolysed to give a compound of Formula XXI (Formula I, R_1 = H, R_3 = -OR_m where R_m is H, R_4= -C(=O)R_Z wherein R_Z = -NR_7R_8 and R_5 and R_6 may be independently selected from hydrogen, alkyl, cycloalkyl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aryl, or aralkyl; or **R_5** and **R_6** may together join to form a cycloalkyl ring).

The condensation of a compound of Formula III with compound of Formula XVII to give a compound of Formula XVIII can be carried out in an organic solvent, for example tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The condensation of

a compound of Formula III with a compound of Formula XVII can be carried out in the presence of an organic base, for example N-methylmorpholine, diisopropylethylamine or triethylamine. The condensation of a compound of Formula III with a compound of Formula XVII can be carried out in the presence of a condensing agent, for example 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride or dicyclohexylcarbodiimide or by a mixed anhydride reaction using chloroformates, for example ethyl chloroformate or isobutyl chloroformate. The hydrolysis of a compound of Formula XVIII (when P is ethyl) to give a compound of Formula XIX can be carried out in a solvent system, for example ethanol, dimethylformamide, tetrahydrofuran, dimethylsulphoxide, dioxane, methanol or water or combinations thereof. The hydrolysis of a compound of Formula XVIII (when P is ethyl) to give a compound of Formula XIX can be carried out in a presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. The condensation of a compound of Formula XIX with a compound of Formula IV to give a compound of Formula XX can be carried out in an organic solvent, for example tetrahydrofuran, dimethylformamide or dimethylsulphoxide. The condensation of a compound of Formula XIX with a compound of Formula IV can be carried out in the presence of an organic base, for example N-methylmorpholine, diisopropylethylamine or triethylamine. The condensation of a compound of Formula XIX with a compound of Formula IV to give a compound of Formula XX can be carried out with condensing agent for example 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride or dicyclohexylcarbodiimide or by a mixed anhydride reaction using chloroformates, for example ethyl chloroformate or isobutyl chloroformate. Alternatively the condensation of a compound of Formula XIX with a compound of Formula IV can also be carried out by mixed anhydride reaction using chloroformates for example, ethyl chloroformate or isobutyl chloroformate. The hydrolysis of a compound of Formula XX (when P is t-butyl) to give a compound of Formula XXI can be carried out in a solvent, for example tetrahydrofuran in water or dichloromethane. The hydrolysis of a compound of Formula XX (when P is t-butyl) to give a compound of Formula XXI can be carried out in the presence of an acid, for example trifluoroacetic acid or hydrochloric acid. The hydrolysis of a compound of Formula XX (when P is ethyl, methyl or benzyl) to give a compound of Formula XXI can be carried out in an organic solvent for example, ethanol, dimethylformamide, tetrahydrofuran, dimethylsulphoxide, dioxane, methanol or water or combinations thereof. The hydrolysis of a compound of Formula XX (when P is ethyl,

methyl or benzyl) can be carried out in a presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide

Compound(s) prepared following the procedure described in Scheme II (Path a) are:

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl-2-{[(4R,5R)-5-(4-methyl-piperazine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid salt with trifluoroacetic acid (Compound No 44)

(S)-2-[{(4R,5R)-5-tert-Butyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 48)

(S)-3-[4-(2,6-Dichloro-benzyloxy-phenyl]-2-[{(4R,5R)-5-(3-methyl-butylcarbamoyl)-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 49)

(S)-3-[4-(2,6,Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(R)-1-phenyl-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 50)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(S)-1-phenyl-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 51)

(S)-1-{(4R,5R)-5-{(S)-1-Carboxy-2-[4-(2,6-dichlorobenzyloxy)-phenyl]-ethyl-carbamoyl}-[1,3]dioxolane-4-carbonyl}-pyrolidine-2-carboxylic acid benzyl ester(Compound No. 52)

(S)-2-[(4R,5R)-{5-Benzyloxy-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 54)

(S)-2-[((4R,5R)-{5-allyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 56)

1-{(4R,5R)-5-[(S)-1-Carboxy-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl}-pyrolidine–2-carboxylic acid (Compound No.57)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(tetrahydro-furan-2-yl-methyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 58)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[2-(1H-indol-3-yl)-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 59)

(S)-3-[4-[(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(2-thiophen-2-yl-ethyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 60)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-[(pyridin-4-ylmethyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No.61)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-(methyl-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No.65)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl)-2-[{4R,5R)-5-[methyl-(1-methyl-piperidine-4-yl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 66)

(S)-3-[4-(2,6-Dichloro-benzyloxy-phenyl]-2-{[(4R,5R)-5-(2-fluoro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino-propionic acid (Compound No. 67)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-methoxy-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 68)

(S)-2-{[(4R,5R)-5-(4-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No.69)

(S)-2-{[(4R,5R)-5-(3-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 70)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-o-tolyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound no.73)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-dimethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino]-propionic acid (Compound No. 74)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl)-2-[{(4R,5R)-5-methyl-carbamoyl-[1,3]dioxolane-4-carbonyl]-amino]- propionic acid (Compound No.75)

(S)-3-[4-[(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-methoxy-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-propionic-acid (Compound No. 76)

(4R,5R)-5-{(S)-1-tert-Butoxycarbonyl-2-[4-(2,6-dichlorobenzyloxy-phenyl]-ethylcarbamoyl]-[1,3]dioxolane-4-carboxylic acid (Compound No.77)

(S)-2,3-[4(2,6-Dichloro-benzyloxy)-phenyl]–2-[{(4R,5R)-5-[2-(4-hydroxy-phenyl)-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic-acid (Compound No. 78)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(pyrrolidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 79)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(R)-3-hydroxy-pyrrolidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 80)

1-((4R,5R)-5-{(S)-1-tert-Butoxycarbonyl-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethylcarbamoyl}-[1,3]dioxolane-4-carbonyl)-pyrrolidine-2-carboxylic acid (Compound No. 81)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(1-hydroxymethyl-propylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 82)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-ethylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 83)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-prop-2-ynylcarbamoyl-[1,3]dioxolane-4-carbonyl]-amino]-propionic acid (Compound No. 84)

Trifluoro acetate salt of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-morpholin-4-yl-ethylcarbamoyl)-[1,3]-dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 85)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(piperidin-1-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 86)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(piperidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 87)

(S)-2-{[(4R,5R)-5-(Bicyclo[2.2.1]hept-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 89)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-isopropyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 91)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-((R)-2-hydrox-1-phenyl-ethylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 97)

(S)-2-{[(4R,5R)-5-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 99)

(S)-2-{[(4R,5R)-5-(2-sec-Butyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 100)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-trifluoromethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 102)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-isopropoxy-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 103)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4-hydroxy-piperidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 104)

(S)-2-{[(4R,5R)-5-Cyclopentylcarbamoyl-[1,3]dioxolane-4-carbonyl]-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 105)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-hexylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 106)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(pyridin-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 108)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(morpholin-4-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 112)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4-hydroxy-cyclohexylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 114)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-heptylcarbamoyl-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 116)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-ethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 117)

(S)-2-{[(4R,5R)-5-(2-Benzyl-5-tert-butyl-2H-pyrazol-3-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 119)

(S)-2-[((4R,5R)-5-cycloheptylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 120)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(5-ethylsulphanyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 121)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4,5-dimethylthiazol-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 123)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4-oxo-piperidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 125)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(indan-5-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 127)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{((4R,5R)-5-phenethylcarbamoyl-[1,3]dioxolane-4-carbonyl]-amino]-propionic acid (Compound No. 128)

(S)-2-({(4R,5R)-5-[(Benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 129)

(S)-2-{[(4R,5R)-5-Butylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 130)

(S)-2-{[(4R,5R)-5-(4-Acetyl-piperazine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzylxoy)-phenyl]-propionic acid (Compound No. 131)

(S)-2-{[(4R,5R)-5-(2-Cyclopentyloxy-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzylxoy)-phenyl]-propionic acid (Compound No. 132)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-octylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 139)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(4-methyl-piperazine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 152)

(S)-2-{[(4R,5R)-5-Cyclopropylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 153)

A compound of Formula XXI can be prepared according to Scheme II, thus a compound of Formula XVIII (Path b) undergoes hydrolysis to give a compound of Formula XXII.

The hydrolysis of a compound of Formula XVIII to give a compound of Formula XXII can be carried out in a solvent system, for example tetrahydrofuran in water or dichloromethane. The hydrolysis of a compound of Formula XVIII to give a compound of Formula XXII can be carried out in the presence of an acid, trifluoroacetic acid or hydrochloric acid. The compound of Formula XXII is condensed with a compound of Formula IV to give a compound of Formula XXI in an organic solvent, for example methanol, ethanol, dimethylformamide or tetrahydrofuran.

Compounds(s) prepared following Scheme II, path b are:

(4R,5R)-5-{(S)-Carboxy-2-[4-(2,6-dichlorobenzyloxy)-phenyl]-ethylcarbamoyl]-[1,3]dioxolane-4-carboxylic acid ethyl ester (Compound No. 46)

(S)-2-[((4R,5R)-5-Carbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 96)

A compound of Formula XXIV can be prepared according to Scheme II thus a compound of Formula XVIII (Path c) is reacted with a compound of Formula IX to give a compound of Formula XXIII, which undergoes hydrolysis to give a compound of Formula XXIV.

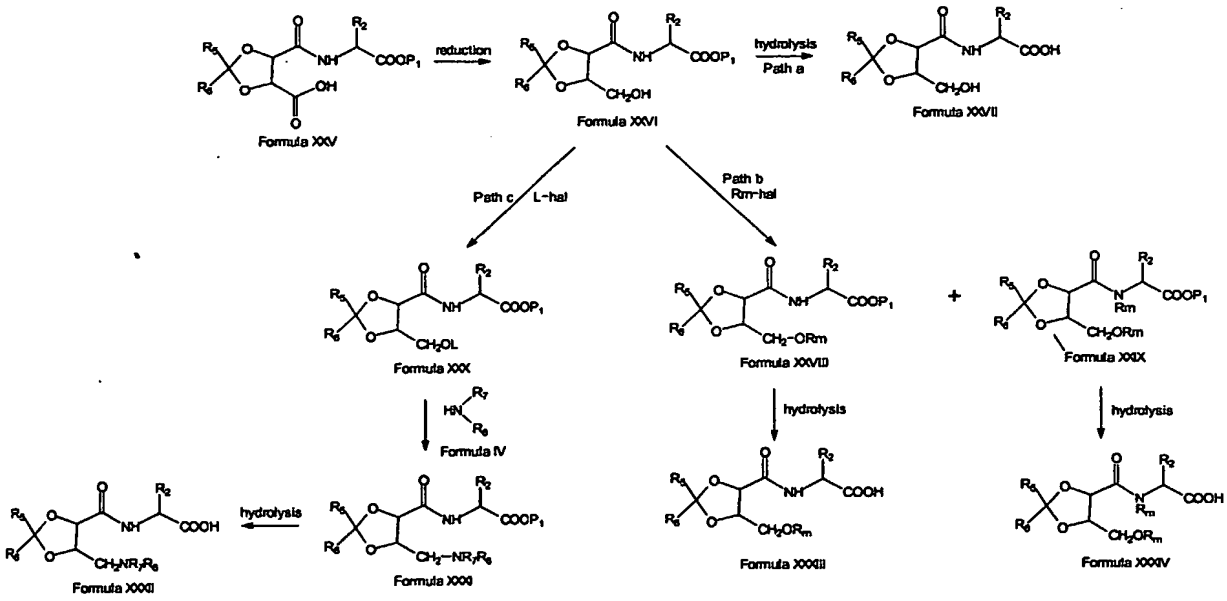
The reaction of a compound of Formula XVIII with a compound of Formula IX to give a compound of Formula XXIII can be carried out in a organic solvent, for example acetone, dichloromethane, tetrahydrofuran, dimethylformamide or acetonitrile. The reaction of a compound of Formula XVIII with a compound of Formula IX can be carried out in the presence of a base, for example sodium hydride, sodium carbonate or potassium carbonate. The hydrolysis of a compound of Formula XXIII (when P is ethyl, methyl or benzyl) to give a compound of Formula XXIV is carried out in a solvent system, for example ethanol, dimethylformamide, dimethylsulphoxide, dioxane, tetrahydrofuran,

methanol or water or combinations thereof. The hydrolysis of a compound of Formula XXIII (when P is ethyl, methyl or benzyl) to give a compound of Formula XXIV can be carried out in the presence of base, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide. Alternatively, when P is t-butyl, the hydrolysis of a compound of Formula XXIII to give a compound of Formula XXIV in the presence of a base for example, lithium hydroxide, sodium hydroxide or potassium hydroxide followed by hydrolysis in the presence of an acid for example trifluoroacetic acid or hydrochloric acid in an organic solvent, for example tetrahydrofuran in water or dichloromethane.

Compound(s) prepared following Scheme II, Path c are:

(4R,5R)-5-{(S)-1-Carboxy-2-[4-(2,6-dichlorobenzyloxy)-phenyl]-ethyl-carbamoyl}-[1,3]dioxolane-4-carboxylic acid (Compound No. 35)

Scheme III



Compounds of Formulae XXVII, XXXIII, XXXIV and XXXII can be prepared according to Scheme III. Thus, a compound of Formula XXV [wherein P_1 is alkyl (for example, ethyl or t-butyl) or aralkyl (for example, benzyl) and R_2, R_5 and R_6 are the same as defined earlier] is reduced to give a compound of Formula XXVI, which is hydrolyzed (Path a) to give a compound of Formula XXVII.

The reduction of a compound of Formula XXV to give a compound of Formula XXVI can be carried out in an organic solvent, for example tetrahydrofuran, dimethoxyethane, diethoxyethane, methanol, dioxane or water or combination thereof. The reduction of a compound of Formula XXV to give a compound of Formula XXVI through

an intermediacy of a mixed anhydride can be carried out in the present of a base, for example N-methylmorpholine, pyridine, triethylamine or diisopropylethylamine with chloroformates, for example ethyl chloroformate or isobutyl chloroformate. The reduction of a compound of Formula XXV to give a compound of Formula XXVI can be carried out with a reducing agent, for example sodium borohydride or sodium cyanoborohydride. The hydrolysis a compound of Formula XXVI (when P_1 is ethyl) to give a compound of Formula XXVII can be carried out in a solvent system, for example tetrahydrofuran, methanol, dioxane, ethanol or water or combinations thereof. The hydrolysis of a compound of Formula XXVI (when P_1 is ethyl) to give a compound of Formula XXVII can be carried out in the presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. The hydrolysis of a compound of Formula XXVI (when P_1 is t-butyl) to give a compound of Formula XXVII can be carried out in an organic solvent, for example, tetrahydrofuran in water or dichloromethane. The hydrolysis of a compound of Formula XXVI (when P_1 is t-butyl) to give a compound of Formula XXVII can be carried out in the presence of an acid, for example, trifluoroacetic acid or hydrochloric acid.

Compound(s) prepared following the procedure described in Scheme III (Path a) include:

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-hydroxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 95)

A compound of Formula XXXIII and XXXIV can be prepared according to Scheme III. Thus a compound of Formula XXVI (Path b) is reacted with a compound Rm-hal [wherein Rm is alkyl and hal is halogen (Cl, Br, I)] to give a compound of Formula XXVIII and XXIX, which are further hydrolyzed to give a compound of Formula XXXIII and XXXIV.

The reaction of a compound of Formula XXVI with a compound Rm-hal to give a compound of Formula XXVIII and XXIX can be carried out in an organic solvent, for example tetrahydrofuran, dimethylformamide, diethyl ether or dioxane. The reaction of a compound of Formula XXVI with a compound Rm-hal to give a compound of Formula XXVIII and XXIX can be carried out in the presence of a base, for example sodium hydride or potassium tert-butoxide. A compound of Formula XXVIII and XXIX (P_1 is t-butyl) can be hydrolyzed to give a compound of Formula XXXIII and XXXIV in the presence of an acid for example trifluoroacetic acid or hydrochloric acid in a solvent system, for example tetrahydrofuran in water or dichloromethane. A compound of

Formula XXVIII and XXIX (when P_1 is ethyl) can be hydrolyzed to give a compound of Formula XXXIII and XXXIV in the presence of a base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide in a solvent system, for example tetrahydrofuran, methanol, dioxane, ethanol or water or combinations thereof.

Compounds prepared following the procedure described in Scheme III (Path b) are:

(S)-2-[((4R,5R)-5-Benzyloxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 101)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-methyl-amino]-propionic acid (Compound No. 126)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 141)

A compound of Formula XXXII can be prepared according to Scheme III. Thus a compound of Formula XXVI (Path c) is reacted with a compound L-hal [wherein OL is mesyl or tosyl and hal is halogen (Cl, Br, I)] to give a compound of Formula XXX, which is reacted with a compound IV (wherein R_7 and R_8 are the same as defined earlier) to give a compound of Formula XXXI, which undergoes hydrolysis to give a compound of Formula XXXII.

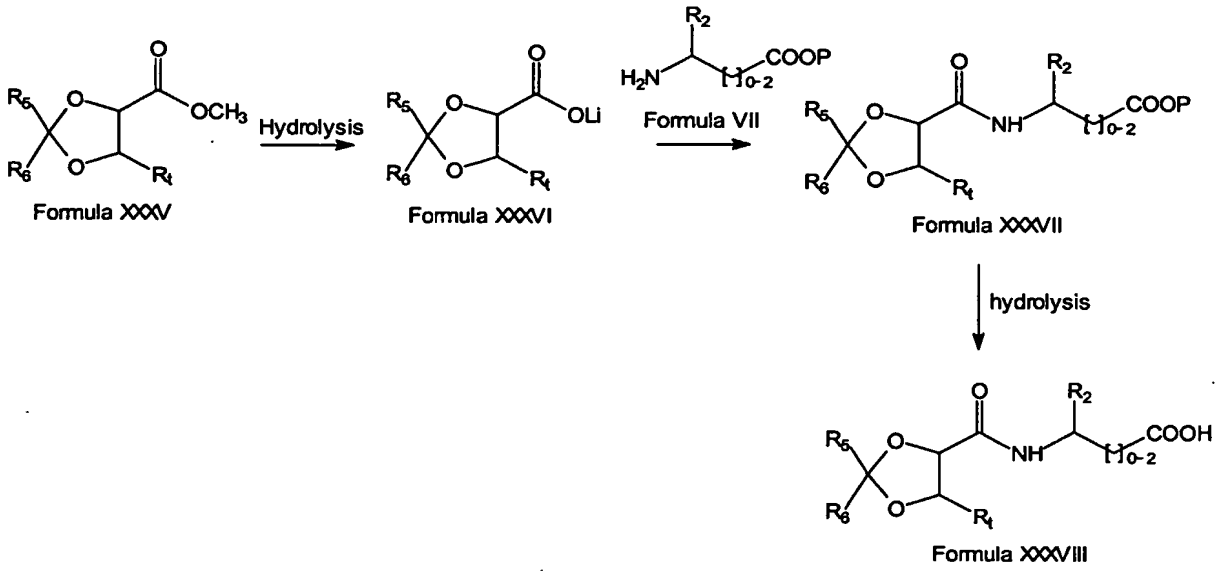
A compound of Formula XXVI is reacted with a compound L-hal to give a compound of Formula XXX in an organic solvent, for example dichloromethane, dichloroethane, chloroform or carbon tetrachloride. The reaction of a compound of Formula XXVI with a compound L-hal to give a compound of Formula XXX can be carried out in the presence of a base, for example triethylamine, pyridine, sodium carbonate, sodium bicarbonate or diisopropylethylamine. The reaction of a compound of Formula XXX with a compound of Formula IV to give a compound of Formula XXXI can be carried out in an organic solvent, for example tetrahydrofuran, dimethylformamide, dioxane or diethyl ether. The reaction of a compound of Formula XXX with a compound of Formula IV to give a compound of Formula XXXI can be carried out in the presence of an organic base, for example diisopropylethylamine, pyridine, N-methylmorpholine or triethylamine. The hydrolysis of a compound of Formula XXXI (when P_1 is t-butyl) to give a compound of Formula XXXII can be carried out in a solvent, for example dichloromethane or tetrahydrofuran in water with an acid, for example trifluoroacetic acid or hydrochloric acid. The hydrolysis of a compound of Formula XXXI (when P_1 is ethyl) to give a compound of Formula XXXII can be carried out in the presence of a base for

example, lithium hydroxide, sodium hydroxide or potassium hydroxide in a solvent system for example, tetrahydrofuran, methanol, dioxane, ethanol or water or combinations thereof.

Compounds(s) prepared following the procedure described in Scheme III (Path c) include:

Trifluoroacetate salt of (S)-3-[4-(2,6-Dichlorobezyloxy)-phenyl]-2-[((4R,5S)-5-pyrrolidin-1-ylmethyl-[1,3]Dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 146).

Scheme IV



A compound of Formula XXXVIII can be prepared according to Scheme IV. Thus a compound of Formula XXXV (wherein R_5 and R_6 are the same as defined earlier R_t is H or CH_3) undergoes hydrolysis to give a compound of Formula XXXVI, which is reacted with a compound of Formula VII to give a compound of Formula XXXVII, which is hydrolyzed to give a compound of Formula XXXVIII.

A compound of Formula XXXV undergoes hydrolysis to give a compound of Formula XXXVI in a solvent system, for example tetrahydrofuran, methanol, dioxane, ethanol or water or combinations thereof in the presence of base, for example lithium hydroxide, sodium hydroxide or potassium hydroxide. The reaction of a compound of Formula XXXVI with a compound of Formula VII to give a compound of Formula XXXVII can be carried out in an organic solvent for example, dimethylformamide, tetrahydrofuran, dioxane or diethyl ether. The reaction of a compound of Formula XXXVI with a compound of Formula VII to give a compound of Formula XXXVII can be carried

out in the presence of an organic base for example, in the presence of an organic base for example, N-methylmorpholine, triethylamine, pyridine or diisopropylethylamine. The reaction of a compound of Formula XXXVI with a compound of Formula VII to give a compound of Formula XXXVII can be carried out with a condensing agent for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or dicyclohexylcarbodiimide. The hydrolysis of a compound of Formula XXXVII to a compound of Formula XXXVIII can be carried out in a solvent system for example, tetrahydrofuran, tetrahydrofuran, methanol, dioxane, ethanol or water or combinations thereof. The hydrolysis of a compound of Formula XXXVII to a compound of Formula XXXVIII can be carried out in the presence of a base for example lithium hydroxide, sodium hydroxide or potassium hydroxide.

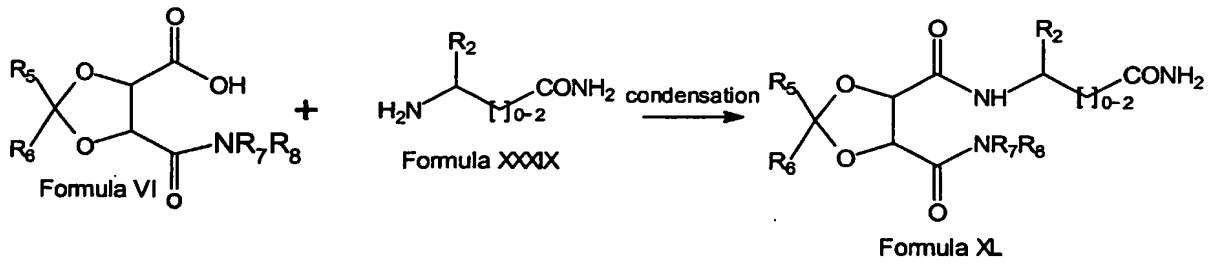
Compound(s) prepared following the procedure described in Scheme IV are:

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((S)-2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 122)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((R)-2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 124)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-2,2,5-trimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 149)

Scheme V



A compound of Formula XL can be prepared according to Scheme V. Thus, a compound of Formula VI is condensed with a compound of Formula XXXIX to give a compound of Formula XL.

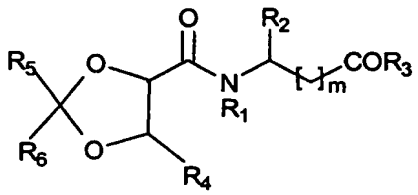
The condensation of a compound of Formula VI with a compound of Formula XXXIX to give a compound of Formula XL can be carried out in an organic solvent for example, tetrahydrofuran, dimethylformamide, dioxane or diethyl ether. The condensation of a compound of Formula VI with a compound of Formula XXXIX to give a compound of Formula XL can be carried out in the presence of a base for example, N-

methylmorpholine, triethylamine, pyridine or diisopropylethylamine. The condensation of a compound of Formula VI with a compound of Formula XXXIX to give a compound of Formula XL can be carried out with condensing agents for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or dicyclohexylcarbodiimide. The reaction of a compound of Formula VI with a compound of Formula XXXIX to give a compound of Formula XL can also be carried out by a mixed anhydride reaction using chloroformates for example, ethyl chloroformate or isobutyl chloroformate.

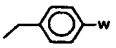
The compounds(s) prepared following the procedure described in Scheme V include:

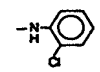
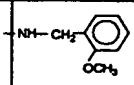
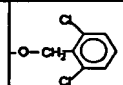
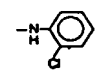
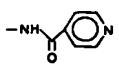
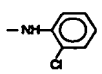
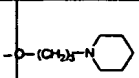
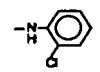
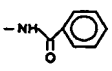
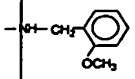
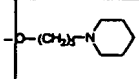
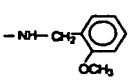
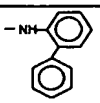
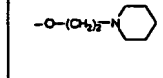
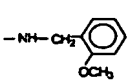
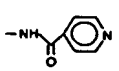
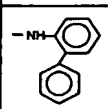
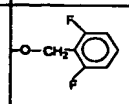
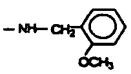
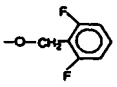
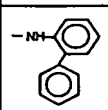
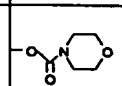
(4R,5R)-[1,3]Dioxolane-4,5-dicarboxylic acid-4-({(S)-1-carbamoyl-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethyl}-amide)-5-[(2-chloro-phenyl)-amide] (Compound No. 118)

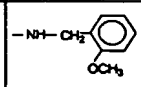
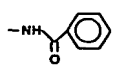
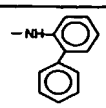
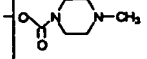
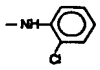
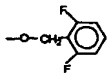
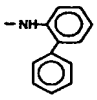
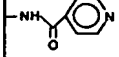
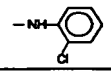
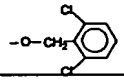
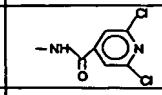
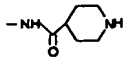
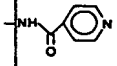
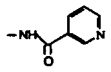
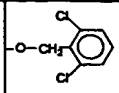
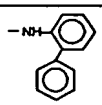
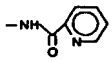
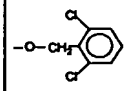
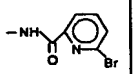
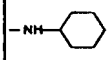
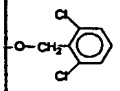
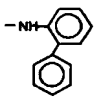
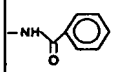
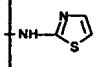
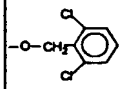
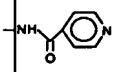
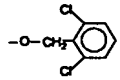
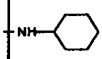
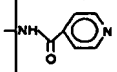
Table I

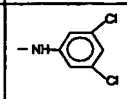
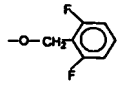
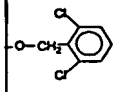
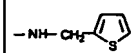
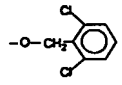
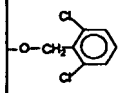
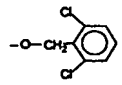
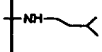
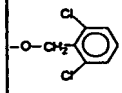
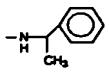
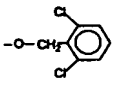
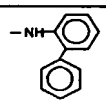
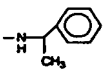
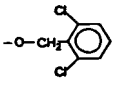
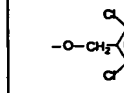
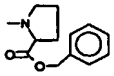
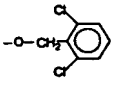
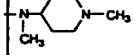
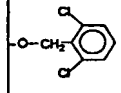
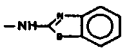
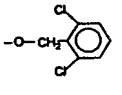
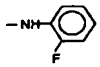
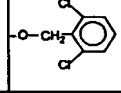
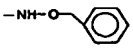
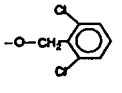
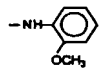
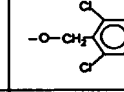
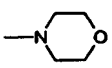
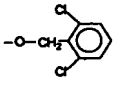
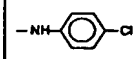
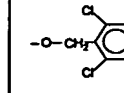
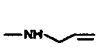
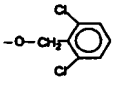
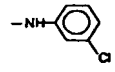
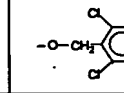


Formula I

(wherein R_1=H, R_2=  , R_3= -OR_m where R_m=H, R_4= -C(=O)R_z, R_5=R_6=H, m=0)

Compound No.	Rz	W	Compound No.	Rz	W
1		OH	10		
2			11 *		
3			12 *		
4		OH	13 *		
5			14		
6			15		

Compound No.	Rz	W	Compound No.	Rz	W
7			16		
8			17		
9			18		
19 **			33 ***		
20			34 *****		
21			36 *		
22			37		
23			38		
24		OH	39		
25			40		
26			41		
27			43		
28			44 **		
29			45		

Compound No.	Rz	W	Compound No.	Rz	W
30			47		
31			48		
32			49		
50			64		H
51 ****			65		
52			66 **		
53			67		
54			68		
55			69		
56			70		
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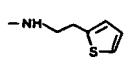
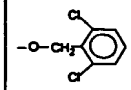
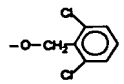
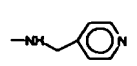
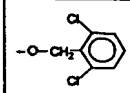
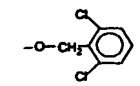
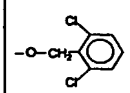
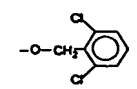
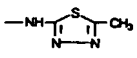
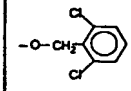
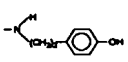
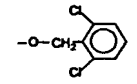
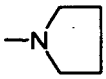
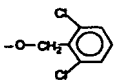
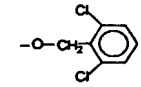
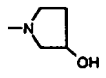
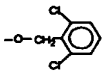
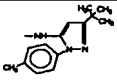
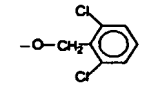
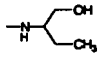
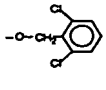
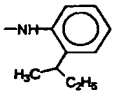
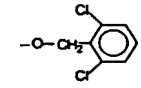
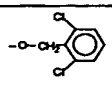
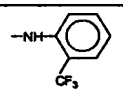
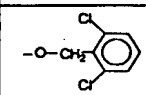
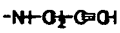
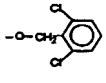
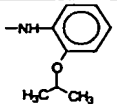
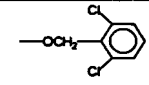
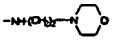
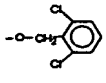
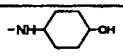
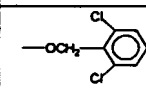
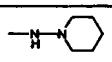
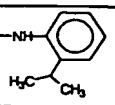
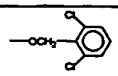
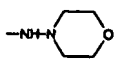
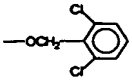
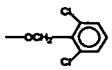
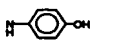
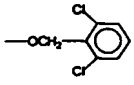
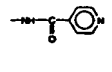
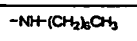
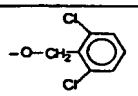
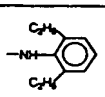
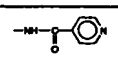
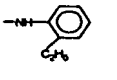
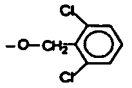
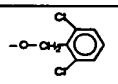
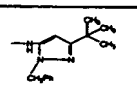
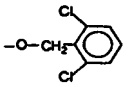
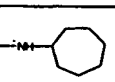
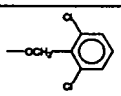
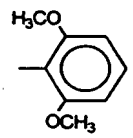
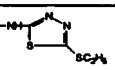
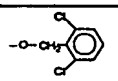
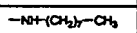
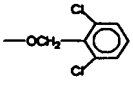
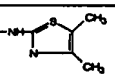
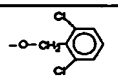
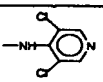
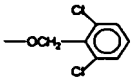
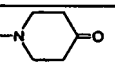
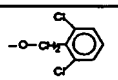
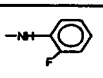
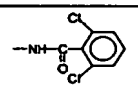
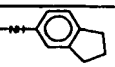
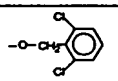
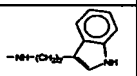
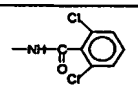
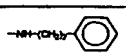
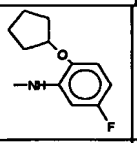
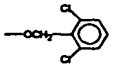
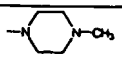
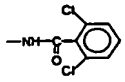
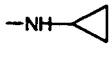
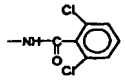
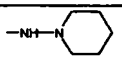
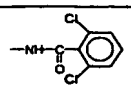
60			74		
61 **			75		
62			76		
63			78		
79			97		
80			99		
82.			100.		
83.	$-NHC_2H_5$		102.		
84.			103.		
85. **			104.		
86.			105.		
87.			106.	$-NH-(CH_2)_5CH_3$	
88.			107.		
89.			108.		
90.			111.		

Compound No.	Rz	W	Compound No.	Rz	W
91.			112.		
92.			114.		
93.			116.		
94.			117.		
96.	$-NH_2$		119.		
120.			137.		
121.			139.		
123.			142.		
125.			143.		
127.			144.		
128.			145.		
129.			147.		
130.			148.		
131.			150.		
132.			151.		

Compound No.	Rz	W	Compound No.	Rz	W
133.			152.		
135.			153.		
136.		-F	154.		

* represents lithium salt of

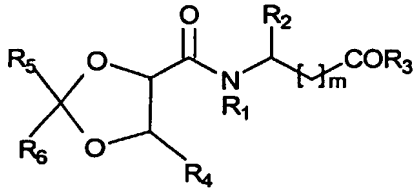
** represents trifluoro acetate salt of

*** diastereomer of Compound No. 2

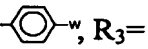
**** represents isomer of Compound No. 50

***** diastereomer of Compound No. 9

Table II



Formula I

(wherein R_1=H, R_2=  , R_3= -OR_m and R_5 = R_6 = H, m=0)

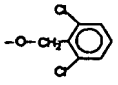
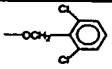
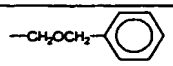
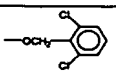
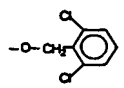
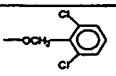
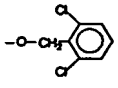
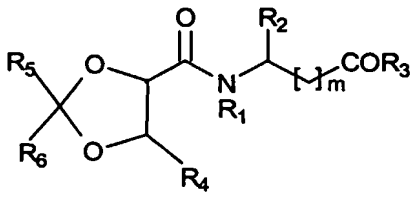
Compound No.	R_4	R_m	W	Compound No.	R_4	R_m	W
35	-COOH	H		95	$-CH_2OH$	H	
42	$-COOC_2H_5$	H	-OH	101		H	
46	$-COOC_2H_5$	H		141	$-CH_2OCH_3$	H	
77	-COOH	t-butyl					

Table III



Formula I

(wherein R_5=R_6=H and m=0)

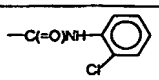
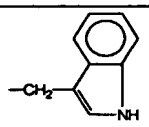
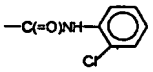
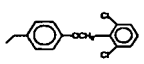
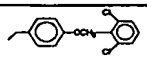
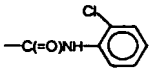
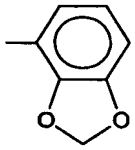
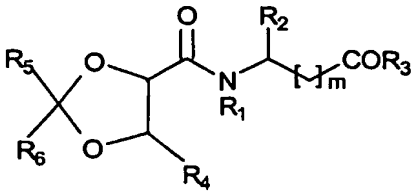
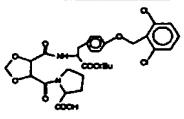
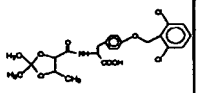
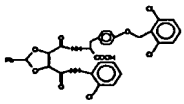
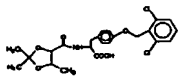
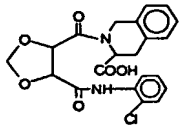
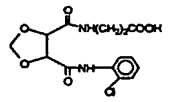
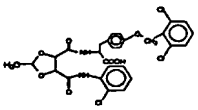
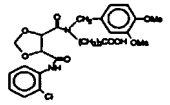
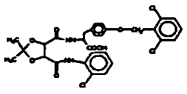
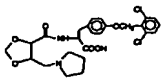
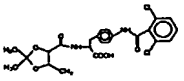
Compound No.	R_4	R_2	R_3	R_1
110.			-OH	H
118.			$-NH_2$	H
126.	$-CH_2OCH_3$		OH	CH_3
134.			OH	H

Table IV



Formula I

Compound No.	Structure	Compound No.	Structure
81.		122. ******	
98.		124.	
109.		138.	
113.		140.	
115.		146. **	
149.			

** represents trifluoro acetate salt of

****** represents a diastereomer of Compound No. 124.

EXPERIMENTAL

General procedure: Synthesis of (4R, 5R)-[1,3]dioxolane-4, 5-dicarboxylic acid diethyl ester (Formula II) The title compound was prepared following the procedure outlined in *Biorg. Med. Chem.* 10, 1567-1580 (2002) starting from diethyl L-tartrate.

Synthesis of (4R,5R)-[1,3]dioxolane-4, 5-dicarboxylic acid monoethyl ester (Formula III) An ethanolic solution of potassium hydroxide (2.68 gm in 100 ml of ethanol) was added dropwise to a solution of diethyl (4R, 5R)-[1,3]dioxolane-4,5-dicarboxylate (20 gm) in ethanol (150 ml), and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and the crude oil was taken in water and extracted with ethyl acetate (2×50 ml). The aqueous layer was then acidified (conc. HCl) and extracted with ethyl acetate (2×200 ml). The combined organic extracts were then washed with water and brine (100 ml) and dried over sodium sulphate. Evaporation of the solvent under vacuo furnished the title compound (8.7g crude) as a sticky solid.
^{1}H NMR ($CDCl_3$, 300 MHz):δ 5.32 (1H, s) & 5.25 (1H, s) [OCH_2O], 4.81 (2H, s, OCH×2), 4.30 (2H, q, J=7.1Hz, OCH_2) and 1.39 (3H, t, J=7.1Hz, CH_3).

SCHEME 1 PATH C PROCEDURE

Example 1: Synthesis of (S)-2-{[(4R, 5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 17)

Step 1: Synthesis of (4R, 5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carboxylic acid ethyl ester.

N-methyl-morpholine (NMM) (265 mg, 2.63 mmol) was added to the compound of Formula III (0.5 g, 2.63 mmol) in dry tetrahydrofuran (10 ml) at -15°C followed by the addition of ethyl chloroformate (285 mg, 2.63 mmol). The reaction mixture was stirred at the same temperature for 30 min. and then 2-aminobiphenyl (444 mg, 2.63 mmol) and p-toluenesulfonic acid (49 mg, 0.263 mmol) were added. The reaction mixture was stirred at -10°C for 30 min. followed by stirring at 0°C for 2 hour and then at room temperature overnight. The reaction was quenched with water and extracted the compound with ethyl

acetate (2×25 ml). The combined organic extract was washed with brine and dried over sodium sulphate and concentrated to obtain the crude residue. The residue was then purified over a silica gel column using 30% ethyl acetate hexane as eluent to obtain the title compound (0.6 gm, 67%) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.45 (1H, s, N*H*), 8.36 (1H, d, J=9Hz) & 7.20-7.50 (8H, m) [aromatic], 5.02 (1H, s) & 4.87 (1H, s) [OCH_2O], 4.86 (1H, d, J=3Hz) & 4.68 (1H, d, J=3Hz) [OC*H*×2], 4.28 (2H, q, J=6Hz, OCH_2) and 1.32 (3H, t, J=6Hz, CH_3).
LCMS (m/e): 342.5 (M+1, 100%).

Step 2: Synthesis of (4R, 5R)-5-(Biphenyl-2-ylcarbamoyl)-[1,3]dioxolane-4-carboxylic acid.

Hydrolysis of the ethyl ester obtained from step 1 above (3.2 gm, 9.3 mmol) in tetrahydrofuran: water: methanol (3:1:1, 10 ml) using lithium hydroxide monohydrate (394 mg, 9.3 mmol) afforded after general aqueous workup and acidification, the title compound (2.7 gm, 93%) as a white solid.
^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.30 (1H, s, N*H*), 7.75 (1H, d, J=7.8Hz) & 7.25-7.50 (8H, m) [aromatic], 5.00 (2H, d, J=3Hz, OCH_2O) and 4.69 (1H, d, J=1.5Hz) & 4.59 (1H, d, J=1.5Hz) [OC*H*×2].

Step 3: Synthesis of Methyl (S)-2-{[(4R, 5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-nitro phenyl)-propionate.

4-Nitro-L-phenylalanine methyl ester hydrochloride (1.24g, 4.7 mmole), N-methylmorpholine (1.19 gm, 11.8 mmol) and hydrobenzotriazole (646 mg, 4.8 mmol) were added to the acid obtained from step 2 above (1.5 g, 4.7 mmol) in dry dimethyl formamide (10 ml) at 0°C. The reaction mixture was stirred at 0°C temperature for 30 min. followed by addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl) (915 mg, 4.8 mmol). The reaction mixture was warmed gradually and stirred at room temperature overnight. The reaction mixture was taken into water (50 ml) and organic compound was extracted with ethyl acetate (2×50 ml). The combined organic layer was washed with water and brine and dried over sodium sulphate (anhydrous). Evaporation of the solvent followed by purification of the residue over a

silica gel column using 2.5% methanol dichloromethane as eluent furnished the title compound (1.78 g, 73%) as a solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.41 (1H, s, N*H*), 8.30 (1H, d, J=6Hz), 8.17 (2H, d, J=9Hz), 7.15-7.50 (11H, m) [aromatic], 4.95 (1H, s), 4.77 (1H, s) [OCH_2O], 4.93 (1H, m, NC*H*), 4.65 (1H, d, J=6Hz) & 4.56 (1H, d, J=6Hz) [OC*H*×2], 3.77 (3H, s, OCH_3) and 3.33 (1H, dd, J=15 and 6Hz) & 3.19 (1H, dd, J=15 and 6Hz) [CH_2Ar].

LCMS (m/e): 520.4 (M+1, 100%).

Step 4: Synthesis of Methyl (S)-3-(4-amino-phenyl)-2-{[(4R, 5R)-5-(biphenyl-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionate.

Palladium on carbon (10% dry, 300 mg) was added to the nitro compound obtained from step 3 above (1.7 gm) in tetrahydrofuran (50 ml), and the reaction mixture was shaken under a hydrogen atmosphere at 50 psi for 3 hour. The reaction mixture was filtered through a celite pad and the filtrate was concentrated to obtain the title compound (1.4 gm, 88%) as a solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (1H, s), 8.32 (1H, d, J=8.1Hz), 6.25-7.50 (8H, m), 6.95 (1H, d, J=8.4Hz), 6.89 (2H, d, J=8.1Hz) & 6.60 (2H, d, J=8.1Hz) [aromatic & N*H*], 4.91 (1H, s) & 4.78 (1H, s) [OCH_2O], 4.81 (1H, m, NC*H*), 4.68 (1H, d, J=3.9 Hz) & 4.64 (1H, d, J=3.6Hz) [OC*H*×2], 3.72 (3H, s, OCH_3) and 2.95-3.10 (2H, m, CH_2Ar).

LCMS (m/e): 490.5 (M+1, 100%).

Step 5: Synthesis of Methyl (S)-2-{[((4R, 5R)-5-biphenyl-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionate.

The aniline obtained from step 4 above (150 mg, 0.31 mmol) in dry dimethyl formamide (2.5 ml) was coupled to isonicotinic acid (37 mg, 0.31 mmol) following the conditions as used for step 3 above, using hydroxybenzotriazole (45 mg, 0.33 mmol), N-methylmorpholine (35 mg, 0.35 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl)(60 mg, 0.32 mmol) to furnish the title compound (110 mg, 61%) as a solid after column purification over silica gel.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.81 (2H, d, J=4.5 Hz), 8.41 (1H, s, N*H*), 8.26 (1H, d, J=6Hz), 7.86 (1H, s, N*H*), 7.70 (2H, d, J=4.5Hz), 7.59 (2H, d, J=7.5Hz), 7.17-7.50 (8H, m), 7.15 (2H, d, J=8.1Hz) & 7.02 (1H, d, J=9Hz) [aromatic], 4.94 (1H, s) & 4.85 (1H, s) [OCH_2O], 4.89 (1H, m, NC*H*), 4.66 (1H, bs) & 4.63 (1H, bs) [OC*H*×2], 3.75 (3H, s, OCH_3) and 3.19 (1H, m) & 3.09 (1H, m) [2H, m, CH_2Ar].

Step 6: Synthesis of (S)-2-{[(4R, 5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid.

The compound obtained from step 5 above (104 mg, 0.1 mmol) was subjected to basic hydrolysis using lithium hydroxide monohydrate (7.6 mg, 0.18 mmol) following the procedure as described in step 2 above furnished after acidic workup the title compound (60 mg, 58%) as a solid.

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.46 (1H, s, N*H*), 9.35 (1H, s, N*H*), 8.78 (2H, d, J=6Hz), 8.30 (1H, d, NH), 7.85 (2H, d, J=9Hz), 7.70 (1H, d, J=6Hz), 7.68 (2H, d, J=9Hz), 7.30-7.45 (8H, m) & 7.23 (2H, d, J=9Hz), 5.00 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.45-4.55 (3H, m, OC*H*×2 and NC*H*) and 3.09 (2H, m, CH_2Ar).

LCMS (m/e): 581.3 (M+1, 100%)

Analogs of (S)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic-acid (Compound No. 17) described below were prepared by replacing the appropriate amine or acid in place of 2-aminobiphenyl or isonicotinic acid, respectively, as applicable in each case.

(S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 2)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.7 (1H, bs, CO_2H), 10.45 (1H, s, N*H*), 9.66 (1H, s, N*H*), 8.78 (2H, d, J=6Hz), 8.41 (1H, d, J=9Hz), 7.86 (2H, d, J=3Hz), 7.79 (1H, d, J=3Hz), 7.68 (2H, d, J=9Hz), 7.52 (1H, d, J=6Hz), 7.36 (1H, t, J=9Hz) & 7.24 (3H, d, J=9Hz) [aromatic], 5.26 (1H, s) & 5.14 (1H, s) [OCH_2O], 4.72 (1H, d, J=3Hz) & 4.67 (1H, d, J=3Hz) [OC*H*×2], 4.51 (1H, m, NC*H*) and 2.95-3.20 (2H, m, CH_2Ar).

LCMS (m/e): 539.0 (M+1, 100%).

(S)-3-(4-Benzoylamino-phenyl)-2-{[(4R,5R)-5-(2-chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 3)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.7 (1H, bs, CO_2H), 10.25 (1H, s, N*H*), 9.72 (1H, s, N*H*), 8.45 (1H, d, J=6Hz), 8.00 (2H, d, J=9Hz) & 7.85 (1H, d, J=9Hz), 7.75 (2H, d, J=9Hz), 7.62 (4H, m), 7.42 (1H, t, J=9Hz) & 7.27 (3H, m) [aromatic], 5.32 (1H, s) & 5.21 (1H, s) [OCH_2O], 4.79 (1H, d, J=3Hz) & 4.73 (1H, d, J=6Hz) [OC*H*×2], 4.57 (1H, m, NC*H*) and 3.00-3.30 (2H, m, CH_2Ar).

LCMS (m/e): 538.4 (M+1, 70%).

(S)-2-{[(4R,5R)-5-(2-Methoxy-benzylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 5)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.46 (1H, s, N*H*), 8.78 (2H, d, J=3Hz), 8.55 (1H, s), 8.31 (1H, d, N*H*), 7.85 (2H, d, J=3Hz), 7.67 (2H, d, J=9Hz), 7.24 (3H, bs), 7.10 (1H, d, J=3Hz), 6.97 (1H, d, J=6Hz) & 6.90 (1H, t, J=6Hz) [aromatic], 5.16 (1H, s) & 5.09 (1H, s) [OCH_2O], 4.51 (2H, s, OC*H*×2), 4.47 (1H, m, NC*H*), 4.27 (2H, s, NCH_2Ar), 3.79 (3H, s, OCH_3) and 2.69-3.20 (2H, m, CH_2Ar).

LCMS (m/e): 549.2 (M+1, 100%).

(S)-3-(4-Benzoylamino-phenyl)-2-{[(4R,5R)-5-(2-methoxy-benzylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 7)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.59 (1H, t), 7.94 (1H, t, J=3.3Hz, N*H*), 7.69 (1H, s), 7.66 (1H, s), 7.50-7.60 (5H, m), 7.09-7.22 (4H, m), 6.90-6.98 (2H, m) [aromatic], 5.16 (1H, s) & 5.09 (1H, s) [OCH_2O], 4.54 (2H, d, J=3.9Hz), 4.46 (1H, m, NC*H*), 4.28 (2H, ABq, J=3.6Hz, NCH_2Ar), 3.79 (3H, s, OCH_3) and 2.95-3.12 (2H, m, CH_2Ar)

LCMS (m/e): 548.3 (M+1, 100%).

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbnyl]-amino}-3-{4-[(2,6-dichloro-pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 18)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.57 (1H, s, CO_2H), 9.34 (1H, s, N*H*), 8.31 (1H, d, N*H*), 8.00 (2H, s), 7.67 (4H, m), 7.23-7.42 (10H, m) [aromatic], 5.00 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.46-4.50 (3H, m, OC*H*×2 and NC*H*) and 2.90-3.20 (2H, m CH_2Ar).

LCMS (m/e): 649.1 (M+1, 100%) and 651.0 (M+3, 55%)

(S)-2-{[(4R,5R)-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[(piperidine-4-carbonyl)-amino]-phenyl}-propionic-acid, salt with trifluoroacetic acid (Compound No.19)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.98 (1H, s, N*H*), 9.38 (1H, s, N*H*), 8.50 (1H, bs, N*H*), 8.29 (2H, m, NH_2), 7.67 (1H, d, J=6Hz), 7.30-7.50 (10H, m) & 7.15 (2H, d, J=9Hz) [aromatic], 5.00 (1H, s), 4.94 (1H, s) [OCH_2O], 4.50 (1H, d, J=3Hz) & 4.42 (2H, m) [OC*H* X 2 and NC*H*], 3.35 (3H, m), 3.07 (1H, m), 2.94 (2H, m) & 2.64 (1H, m) [NCH_2 X 2, CH_2Ar and COC*H*] and 2.12 (2H, m) & 2.06 (2H, m) [CH_2 X 2 (ring)].

LCMS (m/e): 587.2 (M+1, 100%).

(S)-2-{[(4R,5R)-5-(Biphenyl-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[(pyridine-3-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 20)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.40 (1H, s, CO_2H), 9.37 (1H, s, N*H*), 9.09 (1H, s), 8.75 (1H, d, J=3Hz), 8.29 (2H, m), 7.58 (2H, d, J=6Hz), 7.43 (1H, d, J=6Hz), 7.30-7.40 (6H, m) & 7.20 (2H, d, J=9Hz) [aromatic], 5.00 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.52 (1H, d, J=3Hz), 4.45 (1H, d, J=3Hz) [OC*H*×2], 4.44 (1H, m, NC*H*) and 3.20 (2H, m, CH_2Ar).

LCMS (m/e): 581.2 (M+1, 100%)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[(pyridine-2-carbonyl)-amino]-phenyl}-propionic-acid (Compound No. 21)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.58 (1H, s, N*H*), 9.35 (1H, s, N*H*), 8.74 (1H, d, J=6Hz), 8.30 (1H, d, N*H*), 8.15 (1H, d, J=6Hz), 8.07 (1H, t, J=7.8Hz), 7.81 (2H, d, J=9Hz), 7.69 (2H, m), 7.30-7.45 (8H, m) & 7.21 (2H, d, J=9Hz) [aromatic], 5.00 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.51 (1H, d, J=3Hz) & 4.46 (2H, m) [OC*H*×2 and NC*H*] and 2.95-3.17 (2H, m, CH_2Ar).

LCMS (m/e): 581.4 (M+1, 100%)

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-[6-bromo-pyridine-2-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 22)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.35 (1H, s, N*H*), 9.35 (1H, s, N*H*), 8.29 (1H, d, N*H*), 8.13 (1H, d, J=6Hz), 8.00 (1H, t, J=9Hz), 7.91 (1H, d, J=6Hz), 7.76 (2H, d, J=6Hz), 7.70

(1H, d, J=9Hz), 7.30-7.45 (7H, m) & 7.22 (2H, d, J=6Hz) [aromatic], 5.00 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.51 (1H, d, J=3Hz) & 4.47 (2H, m) [OC*H*×2 and NC*H*] and 2.95-3.15 (2H, m, CH_2Ar).

LCMS (m/e): 659.1 (M+1, 85%) and 661.5 (M+3, 100%).

(S)-3-(4-Benzoylamino-phenyl)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 23)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.20 (1H, s, N*H*), 9.35 (1H, s, N*H*), 8.28 (1H, d, NH), 7.94 (2H, d, J=6Hz), 7.68 (2H, d, J=9Hz), 7.56 (2H, m), 7.30-7.55 (12H, m) & 7.19 (2H, d, J=9Hz) [aromatic], 5.01 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.52 (1H, d, J=3Hz) & 4.47 (2H, m) [OC*H*×2 and NC*H*] and 2.95-3.15 (2H, m, CH_2Ar).

LCMS (m/e): 580.5 (M+1, 100%).

(S)-3-{4-[(2,6-Dichloro-pyridine-4-carbonyl)-amino]-phenyl}-2-{[(4R,5R)-5-(2-methoxy-benzylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic-acid (Compound No. 28)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.56 (1H, s, CO_2H), 8.52 (1H, t), 8.29 (1H, s, N*H*), 7.63 (2H, d, J=9Hz), 7.23 (4H, d, J=9Hz), 7.08 (1H, d, J=9Hz), 6.96 (1H, d, J=9Hz), 6.88 (2H, t, J=9Hz) [aromatic], 5.15 (1H, s) & 5.07 (1H, s) [OCH_2O], 4.49 (3H, bs, OC*H*×2 and NC*H*), 4.25 (2H, s, NCH_2Ar), 3.78 (3H, s, OCH_3) and 2.88 (2H, m, CH_2Ar).

LCMS (m/e): 617.1 (M+1, 100%).

(S)-2-{[(4R,5R)-5-(Biphenyl-2-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2-methoxy-benzyl amino)-phenyl]–propionic acid (Compound No 29)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.08 (1H, s, NH), 9.38 (1H, s, N*H*), 8.3 (1H, m, N*H*), 7.0-7.70 (17H, aromatic), 5.01 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.52 (1H, d, J=3Hz) & 4.45 (1H, d) [OC*H*×2], 4.45 (1H, m, NC*H*), 3.89 (3H, s, OCH_3) and 3.06 (2H, m, CH_2Ar)

LCMS (m/e): 610.2 (M+1, 80%)

(S)-3-(4-benzoylaminophenyl)-2-[{(4R,5R)-5-(isopropyl-carbamoyl)-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 43)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.17 (1H, s, N*H*), 8.19 (1H, d, N*H*), 7.93 (3H, m), 7.67 (2H, m), 7.53 (3H, m) & 7.20 (2H, d, J=9Hz) [aromatic], 5.09 (1H, s), 5.06 (1H, s)

[OCH_2O], 4.48 (2H, bs) & 4.37 (1H, d, J=3Hz) [OCH×2 and NCH], 3.89 (1H, m, NCHCH$_3$), 3.03 (2H, m, CH_2Ar) and 1.08 (d, J=3Hz) & 1.07 (d, J=6Hz) [CH_3×2].
LCMS (m/e): 470.1 (M+1, 100%)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(2-methoxy-benzyl carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 151)

^{1}H NMR (DMSO, 300MHz):δ 10.67 (1H, bs), 8.3 (1H, bs), 8.15 (1H, bs), 7.57 (5H, m), 7.20 (4H, m), 6.96 (2H, m), 5.16 (1H, s), 5.10 (1H, s), 4.53 (3H, m), 4.28 (2H, bs), 3.8 (3H, s), 3.33 (2H, m).
LCMS (m/e): 616.42 $(M+1)^+$ [100%], 618.38 $(M+3)^+$ [70%]

SCHEME I, PATH A PROCEDURE

Example 2: (S)-2-{[(4R,5R)-5-(Biphenyl-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 25)

Step 1: Synthesis of Benzyl (S)-2-{[(4R, 5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-hydroxy-phenyl)-propionate.

The compound (4R, 5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carboxylic acid (as prepared in Example 1, Step 2) (1.5 gm, 4.7 mmol) was coupled to L-tyrosine benzyl ester p-toluene sulfonate salt (2.12 gm, 4.7 mmol) following the general procedure as described in Example 1, Step 3) using hydroxybenzotriazole (646 mg, 4.8 mmol), N-methylmorpholine (1.21gm, 12 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl) (915 mg, 4.8 mmol) furnished the title compound (2.2 gm 83%) after purification of the crude residue over a silica gel column using 50% ethyl acetate: hexane solvent mixture as eluent.
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.44 (1H, s, NH), 8.29 (1H, d, J=8.1Hz), 7.20-7.50 (13H, m), 7.01 (1H, d, NH), 6.87 (2H, d, J=8.1Hz) & 6.67 (2H, d, J=8.1Hz) [aromatic], 5.15 (2H, ABq, J=12Hz, OCH_2Ph), 4.86 (1H, s) & 4.73 (1H, s) [OCH_2O], 4.89 (1H, m, NCH), 4.66 (1H, d, J=3.6Hz), 4.58 (1H, d, J=3.6Hz) [OCH×2] and 2.95-3.12 (2H, m, CH_2Ar).
LCMS (m/e): 567.5 (M+1, 100%).

Step 2: Synthesis of Benzyl (S)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionate

Potassium carbonate (98 mg, 0.71 mmol) and 2,6-dichlorobenzyl bromide (93 mg, 0.39 mmol) was added to the phenol obtained from step 1 above (200 mg, 0.35 mmol) in dry acetone (5 ml) and the mixture was refluxed for 5.6 hour. Solvent was evaporated off and the crude residue was taken into water and extracted with ethyl acetate (3×15 ml). The combined organic extracts were washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by purification of the residue over a silica gel column using 40% ethyl acetate: hexane solvent mixture as eluent furnished the title compound (210 mg, 83%) as a white solid.

^{1}HNMR ($CDCl_3$, 300 MHz,): δ 8.41 (14, s, N*H*), 8.36 (1H, d, J=9Hz), 7.20-7.50 (15H, m), 6.89-7.00 (5H, m) [aromatic], 5.22 (2H, s, OCH_2Ar), 5.14 (2H, ABq, J=12Hz, OCH_2Ph), 4.91 (1H, m, NC*H*), 4.88 (1H, s) & 4.75 (1H, s) [OCH_2O], 4.69 (1H, d, J=3Hz) & 4.61 (1H, d, J=3Hz) [OC*H*×2] and 3.10 (2H, t, J=6Hz, CH_2Ar).

LCMS (m/e): 725.5 (M+1, 100%), 727.6 (M+3, 65%), 726.4 (M+2, 38%) & 728.6 (M+4, 35%).

Step 3: Synthesis of (S)-2-{[(4R, 5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid

Lithium hydroxide monohydrate (25 mg, 0.59 mmol) was added to the ester obtained from step 2 above (210 mg, 9.29 mmol) and following the general procedure as outlined in Example 2, Step 2, the title compound was obtained (140 mg, 76%) as a yellow sticky solid.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.34 (1H, s, N*H*), 8.25 (1H, d, N*H*), 7.71 (1H, d, J=7.5Hz), 7.30-7.60 (11H, m), 7.17 (2H, d, J=8.4Hz) & 6.97 (2H, d, J=8.7Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.0 (1H, s) & 4.94 (1H, s) [OCH_2O], 4.42-4.52 (3H, m, NC*H* and OC*H*×2) and 2.93-3.00 (2H, m, CH_2Ar).

LCMS (m/e): 635.4 (M+1, 100%), 637.4 (M+3, 83%).

Analogs of (S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxalane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic-acid (Compound No. 25), which are described below, can be prepared by replacing the appropriate amine or acid.

(S)-3-[4-(2,6-difluoro-benzyloxy)phenyl]-2-{[(4R,5R)-5-(2-methoxy-benzyl-carbamoyl)-[1,3]-dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 6)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 12.7 (1H, bs, CO_2H), 8.51 (1H, d, N*H*), 8.27 (1H, d, N*H*), 7.49 (1H, m), 7.05-7.20 (6H, m) & 6.80-6.98 (4H, m) [aromatic], 5.13 (1H, s), 5.05 (1H, s) & 5.02 (2H, s) [OCH_2O and OCH_2Ar], 4.50 (2H, d, J=3.9Hz, OC*H*×2), 4.47 (1H, m, NC*H*), 4.24 (2H, Abq, J=5.7Hz, NCH_2Ar), 3.76 (3H, s, OCH_3) and 2.90-3.32 (2H, m, CH_2Ar).

LCMS (m/e): 571.1 (M+1, 100%).

2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-difluoro-benzyloxy)-phenyl]-propionic acid (Compound No. 8)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 2.97-3.07 (2H, m, $ArCH_2$), 4.46-4.68 (1H, m, NHC*H*CO), 4.63-4.68 (2H, OC*H*CO×2), 5.06 (2H, s, $ArCH_2O$), 5.11-5.13 (1H, m) and 5.23-5.24 (1H, m) [OCH_2O], 6.89-6.95 (3H, m), 7.09-7.19 (4H, m), 7.26-7.38 (2H, m), 7.49-7.54 (2H, m) [aromatic].

LCMS (m/e): 561.3 (M+1)

(S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 9)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.73 (1H, s, N*H*), 7.84 (1H, d, J=8.1Hz), 7.72 (1H, bs, N*H*), 7.40-7.55 (4H, m), 7.36 (1H, t, J=7.2 Hz), 7.23 (1H, t, J=7.8Hz), 7.07 (2H, d, J=8.4Hz) & 6.87 (2H, d, J=8.4Hz), 5.22 (1H, s) & 5.15 (3H, m) [OCH_2O and OCH_2Ar], 4.77 (1H, d, J=4.2Hz) & 4.64 (1H, d, J=4.2 Hz), 3.79 (1H, m, NC*H*) and 2.95-3.10 (2H, m, CH_2Ar).

LCMS (m/e): 593.2 (M+1, 90%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-methoxy-benzyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No.10)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.7 (1H, bs, CO_2H), 8.56 (1H, s, N*H*), 8.31 (1H, d, N*H*), 7.56 (2H, dd, J=8.4 and 1.2Hz), 7.48 (1H, dd, J=6.9 and 2.1Hz), 7.05-7.25 (4H, m) & 6.85-7.00 (4H, m) [aromatic], 5.17 (3H, d, J=3Hz) & 5.09 (1H, s) [OCH_2Ar and OCH_2O], 4.54 (1H, d, J=3.9Hz) & 4.50 (1H, d, J=3.9Hz) [OC*H*×2], 4.48 (1H, m, NC*H*), 4.27 (2H, ABq, J=5.74Hz, NCH_2Ar), 3.79 (3H, s, OCH_3) and 2.95-3.10 (2H, m, CH_2Ar).

LCMS (m/e): 603.3 (M+1, 100%).

Lithium salt of (S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(3-piperidin-1-yl-propoxy)-phenyl]-propionate (Compound No.11)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.80 (1H, d, J=7.9Hz), 7.63 (1H, d, J=6Hz), 7.50 (1H, d, J=7.78Hz), 7.32 (1H, t, J=7.66Hz), 7.19 (1H, t), 7.00 (2H, d, J=6.69Hz), 6.71 (2H, d, J=8.3Hz) [aromatic], 5.19 (1H, d, J=4.35Hz) & 5.12 (1H, s) [OC*H*$_2$O], 4.71 (1H, s) & 4.59 (1H, d, J=3.85Hz), [OC*H*×2], 3.91 (3H, ABq, J=5.1Hz) (NC*H* and OC*H*$_2$), 2.99 (2H, m, C*H*$_2$Ar), 2.35 (6H, m, NC*H*$_2$), 1.81 (2H, t, J=6.4Hz) and 1.47 (4H, bs) & 1.46 (2H, bs) [C*H*$_2$×3 (ring)].

LCMS (m/e): 560.3 (M+1, 100%).

Lithium salt of (S)-2-{[(4R,5R)-5-(2-Methoxy-benzyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(3-piperidin-1-yl-propoxy)-phenyl]-propionate (Compound No. 12)

^{1}H NMR (TFA-d, 300 MHz): δ 7.52 (1H, t, J=9Hz), 7.40 (3H, t, J=6Hz), 7.17 (2H, t, J=9Hz) & 7.03 (2H, t, J=6Hz), 5.40 (2H, s, OC*H*$_2$O), 5.22 (1H, m, NC*H*), 5.01 (2H, s, OC*H*×2), 4.78 (2H, s, NC*H*$_2$Ar), 4.43 (2H, s, OC*H*$_2$), 4.11 (3H, s, OC*H*$_3$), 4.03 (2H, bs, NC*H*$_2$), 3.65 (3H, m) & 3.33 (1H, m) [NC*H*$_2$×2], 3.16 (2H, bs, C*H*$_2$Ar), 2.54 (2H, m, OCH$_2$C*H*$_2$) and 2.06-2.35 (6H, m, C*H*$_2$×3 (ring)).

LCMS (m/e): 570.3 (M+1, 100%).

Lithium salt of (S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxalane-4-carbonyl]-amino}-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-propionate (Compound No. 13)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.38 (1H, s, N*H*), 7.68 (1H, d, J=6Hz), 7.51 (1H, d, J=6Hz), 7.30-7.50 (7H, m), 6.97 (2H, d, J=6Hz) & 6.71 (2H, d, J=9Hz) [aromatic], 4.96 (1H, s) & 4.90 (1H, s) [OC*H*$_2$O], 4.54 (1H, d, J=3Hz) & 4.37 (1H, d, J=3Hz) [OC*H*×2], 3.97 (2H, t, J=6Hz, OC*H*$_2$CH$_2$), 3.85 (1H, ABq, J=3Hz, NC*H*), 2.96 (2H, m, NC*H*$_2$) & 2.61 (2H, t, J=6z, NC*H*$_2$), 2.40 (4H, t, J=3Hz, NC*H*$_2$), 1.48 (4H, t, J=6Hz) and 1.36 (2H, t, J=6Hz) [C*H*$_2$×3 (ring)].

LCMS (m/e): 588.2 (M+1, 100%) (free acid).

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-difluoro-benzyloxy)-phenyl]-propionic acid (Compound No. 14)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.33 (1H, s, N*H*), 8.23 (1H, d, N*H*), 7.69 (1H, m), 6.94-7.50 (13H, m) & 6.92 (2H, t, J=6Hz) [aromatic], 5.06 (2H, s, OCH_2Ar), 4.99 (1H, s) & 4.93 (1H, s) [OCH_2O], 4.46 (3H, m, NC*H* and OC*H*×2) and 2.94-3.35 (2H, m, CH_2Ar).
LCMS (m/e): 603.3 (M+1, 100%).

Morpholine-4-carboxylic acid 4-((S)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-2-carboxy-ethyl)-phenyl ester (Compound No. 15)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.33 (1H, s, N*H*), 8.20 (1H, s, N*H*), 7.70 (1H, d, J=6Hz), 7.30-7.50 (8H, m), 7.20 (2H, d, J=9Hz) & 7.01 (2H, d, J=6Hz) [aromatic], 4.98 (1H, s) & 4.92 (1H, s) [OCH_2O], 4.51 (1H, d, J=3Hz) & 4.46 (1H, d, J=3Hz) [OC*H*×2], 4.41 (1H, m, NC*H*), 3.63 (8H, d, J=3Hz, OCH_2×2 and NCH_2×2) and 2.95-3.20 (2H, m, CH_2Ar).
LCMS (m/e): 590.1 (M+1, 50%) and 607.1 (M+18, 100%).

4-Methyl-piperazine-1-carboxylic acid 4-((S)-2-{[(4R,5R)-5-(biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-2-carboxy-ethyl)-phenyl ester (Compound No. 16)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.34 (1H, s, N*H*), 8.12 (1H, d, N*H*), 7.70 (1H, d, J=7.8Hz), 7.25-7.50 (8H, m), 7.19 (2H, d, J=8.4Hz) & 6.98 (2H, d, J=8.1Hz) [aromatic], 4.98 (1H, s) & 4.92 (1H, s) [OCH_2O], 4.51 (1H, d, J=2.7Hz) & 4.45 (1H, d, J=3.3Hz) [OC*H*×2], 4.33 (1H, m, NC*H*), 3.64 (2H, m) & 3.57 (2H, m) [NCH_2×2], 3.10 (1H, m) & 3.00 (1H, m) [CH_2Ar], 2.35 (4H, bs, NCH_2×2) and 2.22 (3H, s, N-CH_3).
LCMS (m/e): 603.3 (M+1, 100%).

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2-chloro-benzyloxy)-phenyl]-propionic-acid (Compound No. 26)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.34 (1H, s, N*H*), 8.23 (1H, d, N*H*), 7.70 (1H, d, J=7.8Hz), 7.30-7.60 (12H, m), 7.15 (2H, d, J=8.4Hz) & 6.92 (2H, d, J=8.4Hz) [aromatic], 5.11 (2H, s OCH_2Ar), 4.99 (1H, s) & 4.93 (1H, s [OCH_2O], 4.40-4.49 (3H, m, OC*H*×2 and NC*H*) and 2.90-3.09 (2H, m, CH_2Ar).
LCMS (m/e): 601.6 (M+1, 100%), 602.5 (M+2, 35%).

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-prop-2-ynyloxy-phenyl)-propionic-acid (Compound No. 27)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.45 (1H, s, N*H*), 8.28 (1H, d), 6.88-7.47 (13H, m) [aromatic & N*H*], 4.54-4.90 (7H, m, OCH_2O, OC*H* X 2, NC*H*, OCH_2C), 3.02-3.25 (2H, m, CH_2Ar) and 2.49 (1H, d, J=3Hz, C*H* (alkyne)).
LCMS (m/e): 515.5 (M+1, 100%).

(S)-2-{(4R,5R)-5-(3,5-Dichlorophenyl-carbamoyl)-[1,3]dioxolane-4-carbonoyl]-amino}-3-[4-(2,6-difluoro-benzyloxy]-phenyl]-propionic-acid (Compound No. 30)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.19 (s), 7.51 (m), 7.31 (s), 7.15 (m) & 6.92 (d, J=9Hz, aromatic], 5.21 (1H, s) & 5.13 (1H, s) [OCH_2O], 5.05 (2H, s, OCH_2Ar), 4.66 (1H, d) & 4.62 (1H, d) [OC*H*x2], 4.47 (1H, m, NC*H*) and 3.01 (2H, m, CH_2Ar).
LCMS (m/e): 595.1 (M+1, 100%) and 597.0 (M+3, 95%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-phenyl-carbamoyl-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (compound No. 32)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.14 (1H, s, N*H*), 8.20 (1H, d, N*H*), 6.90-7.70 (12H, m, aromatic), 5.22 (1H, s) & 5.14 (1H, s) [OCH_2O], 5.17 (2H, s, OCH_2Ar), 4.66 (1H, d, J=3Hz) & 4.61 (1H, d, J=3Hz) [OC*H*×2], 4.43 (1H, m, NC*H*) and 3.34 (2H, m, CH_2Ar).
LCMS (m/e): 558.7 (M+1, 100%) and 561.3 (M+3, 70%).

(S)-3-[4-2-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(morpholine-4-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino-propionic acid (Compound No.55)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.55 (2H, d, J=7.5 Hz), 7.46 (1H, m), 7.18 (2H, d, J=7.8Hz) & 6.97 (2H, d, J=7.5 Hz) [aromatic] 5.21 (2H, s, OCH_2Ar), 5.12 (1H, s) & 5.03 (1H, s) [OCH_2], 4.45-4.70 (5H, m, OC*H* x 2, NC*H* and OCH_2 (ring))], 3.35-3.60 (6H, m) [OCH_2 and NCH_2 x 2 (ring)] and 3.11 (1H,m) & 3.00 (1H,m) [CH_2Ar].
LCMS (m/e): 553.5 (M+1,100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(3,5-dichloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic-acid (Compound No. 71)

^{1}HNMR(DMSO-d_6, 300 MHz) δ 10.43 (1H, s, N*H*), 8.35 (1H, d, N*H*), 7.80 (2H, d, J=3Hz), 7.55 (2H, d, J=9Hz), 7.45 (1H, m), 7.31 (1H, s), 7.19 (2H, d, J=9Hz) & 6.95 (2H, d, J=9Hz) [aromatic], 5.22 (1H, s) & 5.14 (1H, s) [OCH_2O], 5.17 (2H, s, OCH_2Ar), 4.68 (1H, d, J=3Hz) & 4.62 (1H, d, J=3Hz) [OC*H* X 2], 4.49 (1H,m NC*H*) and 3.02 (2H, m, CH_2Ar)

SCHEME I, PATH B PROCEDURE

Example 3: (S)-2-{[(4R,5R)-5-(Bis-thiophen-2-ylmethyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 88)

Step a: Synthesis of (4R,5R)-5-(bis-thiophen-2-ylmethyl-carbamoyl)-[1,3]dioxolane-4-carboxylic acid ethyl ester.

To a solution of the compound of Formula III (1 g) in tetrahydrofuran (20ml) at –20° C, was added N-methyl morpholine (1.06 g) and stirred the reaction mixture for 10 minutes at the same temperature. To it was added ethyl chloroformate (0.57 g) and stirred the reaction mixture for 20 minutes followed by the addition of p-toluene sulphonic acid (95 mg) and bis-thiophene-2-ylmethyl amine (1.29 g). The reaction mixture was stirred for 30 minutes at -20°C for 30 minutes followed by stirring at 0°C for 3 hours and subsequently overnight at room temperature. The reaction mixture was diluted with ethyl acetate and water. The organic layer was washed with water & brine and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 20% ethyl acetate in hexane as eluent to furnish the title compound (22.5 g).

Step b: Synthesis of (4R,5R)-5-(bis-thiophen-2-ylmethyl-carbamoyl)-[1,3]dioxolane-4-carboxylic acid

To the solution of the compound obtained from step a above (750 mg) in tetrahydrofuran:methanol:water (3:1:1) was added lithium hydroxide monohydrate (124 mg) and stirred the reaction mixture for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue thus obtained was taken in water and acidified with concentrated hydrochloric acid. The organic layer was extracted with ethyl acetate, washed with water and brine. The organic layer was concentrated under reduced pressure to furnish the title compound (440 mg).

Step c: Synthesis of (S)-2-{[(4R,5R)-5-(bis-thiophen-2-ylmethyl-carbamoyl)-[1,3] dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]propionic acid methyl ester.

To a solution of the compound obtained from step a above (322 mg) in dimethylformamide (5 ml) at 0°C, was added N-methylmorpholine (0.21 g), hydroxybenzotriazole (0.105 mg) and 2-amino-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid methyl ester (Bioorg. & Med Chem Letters 12(2002) 1591-1594) (250 mg). The reaction mixture was stirred for 30 minutes at same temperature and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (149 mg) was added. The reaction mixture was warmed to room temperature, diluted with water and ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure to furnish the title compound (145 mg).

Step d: Synthesis of (S)-2-{[(4R,5R)-5-(Bis-thiophen-2-ylmethyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 88)

To a solution of the compound obtained from step c above (163 mg) in tetrahydrofuran:methanol:water (3:1:1), was added lithium hydroxide monohydrate (10 mg). The reaction mixture was stirred for 2 hours and concentrated under reduced pressure. The residue thus obtained was taken in water, washed with ethyl acetate. The aqueous layer was acidified with sodium bisulphate and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound (120 mg).

^{1}H NMR (DMSO, 300MHz):δ 8.3 (1H, m), 7.57-7.42 (5H, m), 7.15 (2H, d, 9Hz), 7.05-6.91 (6H, m), 5.14 (4H, m), 4.95 (1H, d, 6Hz), 4.88 (1H, bs), 4.78 (1H, d, 6Hz), 4.62 (2H, s), 4.5 (2H, m), 3.06-2.98 (2H, m).
LCMS (m/e): 675.11 (M^+, 100%), 677.13 (M+Z, 70%), 678.09 (M+3, 30%).

The analogues of (S)-2-{[(4R,5R)-5-(bicyclo[2.2.1]hept-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No.

88) described below, can be prepared by condensing appropriate amine and an acid, respectively, as applicable in each case.

(S)-2-{[(4R,5R)-5-(2-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-hydroxy-phenyl)-propionic acid (Compound No. 1)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.5 (1H, bs, CO_2H), 9.67 (1H, s, NH), 9.22 (1H, bs, OH), 8.31 (1H, d, NH), 7.78 (1H, d, J=7.9Hz), 7.53 (1H, d, J=7.9Hz), 7.35 (1H, t, J=7.5 Hz), 7.26 (1H, t, J=7.6Hz), 7.00 (2H, t, J=7.9Hz) & 6.65 (2H, d, J=7.7Hz) [aromatic], 5.25 (1H, s) & 5.13 (1H, s) [OCH_2O], 4.70 (1H, d, J=3.4Hz), 4.66 (1H, d, J=3.3 Hz) [OCH×2], 4.41 (1H, m, NCH) and 2.85-3.00 (2H, m, CH_2Ar).

(S)-3-(4-Hydroxy-phenyl)-2-{[(4R,5R)-5-(2-methoxy-benzyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 4)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.44 (1H, t, NH), 8.05 (1H, d, NH), 7.22 (1H, t, J=7.41Hz), 7.13 (1H, d, J=7.3Hz), 6.99 (2H, d, J=8.24Hz), 6.92 (2H, m), 6.65 (2H, d, J=8.1Hz), 5.16 (1H, s) & 5.10 (1H, s) [OCH_2O], 4.55 (1H, d, J=3.9Hz), 4.51 (1H, d, J=3.83Hz) [OCH×2], 4.46 (1H, m, NCH), 4.31 (2H, ABq, J=5.7Hz, NCH_2Ar), 3.82 (3H, s, OCH_3) and 2.90-3.00 (2H, m, CH_2Ar).

LCMS (m/e): 445.4 (M+1, 100%).

(S)-2-{[(4R,5R)-5-(Biphenyl-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-hydroxyl-phenyl)-propionic acid (Compound No. 24)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (1H, s, NH), 8.21 (1H, d, J=8.4Hz), 7.10-7.43 (9H, m), 6.95 (2H, d, J=8.1Hz) & 6.69 (2H, d, J=8.1Hz) [aromatic], 4.86 (s) & 4.71 (1H, s) [OCH_2O], 4.81 (1H, m, CH), 4.65 (1H, d, J=3.6 Hz) & 4.57 (1H, d, J=3.9Hz, CH×2] and 2.9-3.10 (2H, m, CH_2Ar).

LCMS (m/e): 477.5 (M+1, 100%).

(S)-3-(4-(2,6-Dichlorobenzyloxy)-phenyl]-2-[{(4R,5R)-5-[thiophen-2-yl-methyl)-carbamoyl]-[1,3]dioxolane-4-carbamoyl}-amino]-propionic acid (Compound No. 31)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.81 (1H, t, NH), 8.21 (1H, m, NH), 7.40-7.55 (3H, m), 7.33 (1H, d, J=3.9Hz), 7.17 (2H, d, J=8.4Hz) & 6.93 (4H, m) [aromatic], 5.19 (2H, s,

OCH_2Ar), 5.12 (1H, s), 5.10 (1H, s) [OCH_2O], 4.54 (1H, d, J=3.6Hz) & 4.47 (4H, bd) [OC*H*×2, NC*H*, NCH_2Ar] and 3.05 (2H, m, CH_2Ar).

LCMS (m/e): 579.1 (M+1, 100%) and 581.0 (M+3, 80%).

(S)-2-{[(4S, 5S)-5-(2-Chlorophenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridin-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 33)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.63 (1H, s, N*H*), 8.78 (2H, d, J=3Hz), 8.40 (1H, d, J=6Hz), 7.85 (2H, d, J=6Hz), 7.78 (1H, d, J=9Hz), 7.68 (2H, d, J=9Hz), 7.52 (1H, d, J=9Hz), 7.36 (1H, t) & 7.23 (3H, d, J=6Hz) [aromatic and N*H*], 5.25 (1H, s) & 5.03 (1H, s) [OCH_2O], 4.71 (1H, d, J=3Hz) & 4.64 (1H, d, J=3Hz) & 4.52 (1H, m, NC*H*) and 2.95-3.20 (2H, m, CH_2Ar)

LCMS (m/e): 539.2 (M+1, 100%)

(S)-2-(4S,5S)-5-(Chlorophenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichlorobenzloxy-phenyl]-propionic acid (Compound No. 34)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.6 (1H, s, N*H*), 8.36 (1H, d, N*H*), 7.80 (1H, d, J=6.9Hz), 7.16-7.60 (8H, m) & 6.97 (2H, d, J=8.7Hz) [aromatic], 5.24 (1H, s) & 5.02 (1H, s) [OCH_2O], 5.19 (2H, s, OCH_2Ar), 4.70 (1H, d, J=3.6Hz) & 4.59 (1H, d, J=3.6Hz) [OC*H*×2], 4.51 (1H, m, C*H*CO) and 2.95-3.20 (2H, m CH_2Ar).

LCMS (m/e): 593 (M+1, 80%) and 595.0 (M+3, 100%).

Lithium salt of (S)-2-[{(4R,5R)-5-Cyclopropyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichlorobenzyloxy)-phenyl]-propionate (Compound No. 36)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.25 (1H, d, N*H*), 7.50 (4H, m), 7.06 (2H, d, J=8.1Hz) & 6.86 (2H, d, J=8.1Hz) [aromatic and N*H*], 5.16 (1H, s) & 5.06 (1H, d, J=3Hz) [OCH_2O], 4.48 (1H, d, J=3.9Hz) & 4.39 (1H, d, J=3.6Hz) [OC*H*×2], 3.98 (1H, m, NC*H*), 3.03 (2H, m, CH_2Ar), 2.70 (1H, t, J=3.6Hz, NC*H* (ring)) and 0.62 (2H, bs) & 0.51 (2H, bs) [CH_2 (ring)×2].

LCMS (m/e): 523.4 (M+1(free acid), 100%).

(S)-2-[{(4R,5R)-5-Cyclohexane-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 37)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.23 (1H, d, N*H*), 7.90 (1H, m, N*H*), 7.40-7.60 (3H, m), 7.16 (2H, m) & 6.95 (2H, d, J=6Hz), [aromatic], 5.19 (2H, s, OCH_2Ar), 5.08 (1H, s) & 5.06 (1H, s) [OCH_2O], 4.26-4.50 (4H, m, OC*H*×2, NC*H* and NC*H* and NC*H* (ring)), 3.00 (2H, m, CH_2Ar) and 1.50-1.10 (10H, m, CH_2×5 (ring)).

LCMS (m/e): 565.3 (M+1, 100%) and 567.3 (M+3, 35%).

(S)-3-[4-(2,6-Dichlorobenzyloxy)-phenyl]-2-{([4R,5R)-5-(thiazol-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 38)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 12.7 (1H, bs, CO_2H), 12.3 (1H, bs, NH), 8.34 (1H, bs, N*H*), 6.90-7.60 (9H, m, aromatic), 6.21 (1H, s) & 5.12 (1H, s) [OCH_2O], 5.17 (2H, s, OCH_2Ar), 4.73 (1H, bs) & 4.69 (1H, d, J=3Hz) [OC*H*×2], 4.46 (1H, bs, NC*H*) and 3.02 (2H, m, CH_2Ar).

(S)-2-{[(4R,5R)-5-(Cyclopropyl-carbamoyl)-[1,3]dioxolane-4-carbonylamino]-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 39)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.44 (1H, s, CO_2H), 8.77 (2H, d, J=6Hz), 8.23 (1H, d, J=3Hz), 7.85 (2H, d, J=6Hz), 7.73 (1H, bs), 7.63 (2H, d, J=9Hz) & 7.17 (2*H*, d, J=9Hz) [aromatic and 2 N*H*], 5.05 (2H, s, OCH_2O), 4.49 (1H, d, J=3Hz), 4.37 (1H, d, J=3Hz), 4.22 (1H, m, NC*H*CO), 2.90-3.10 (2H, m, CH_2Ar), 2.69 (1H, m, NC*H* (ring), 0.61 (2H, m) & 0.50 (2H, m) [CH_2 × 2(ring)].

LCMS (m/e): 469.2 (M+1, 100%).

(S)-2-[{(4R,5R)-5-Cyclohexyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic-acid (Compound No. 40)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.42 (1H, s, CO_2H), 8.76 (2H, d, J=3Hz), 8.16 (1H, d, J=6Hz), 7.95 (1H, d, J=9Hz), 7.85 (2H, d, J=3Hz), 7.67 (2H, d, J=9Hz) & 7.21 (2H, d, J=9Hz) [aromatic and N*H*], 5.09 (1H, s) & 5.06 (1H, s) [OCH_2O], 4.46 (1H, d, J=6Hz) & 4.38 (1H, d, J=3Hz), 1.11-1.70 (10H, m, CH_2 (ring)×5

LCMS (m/e): 511.4 (M+1, 100%)

(S)-2-{[4R,5R)-5-(3,5-Dichloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbamoyl]-amino}-3-{4-[(pyridine-4-carbonyl-amino]-phenyl}-propionic acid (Compound No. 41)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.46 (1H, d, N*H*), 8.79 (1H, s), 7.00-8.40 (12H) [aromatic and N*H*], 5.21 (1H, s), 5.13 (1H, s) [OCH_2O], 4.67 (1H, bs) & 4.63 (1H, d, J=3Hz), [OC*H*×2], 4.50 (1H, bs, NC*H*) and 3.02 (2H, m, CH_2Ar).
LCMS (m/e): 573.4 (M+1,100%)

(S)-(4R,5R)-5-[1-Carboxy-3-[4-(hydroxy-phenyl)-ethyl-carbamoyl]-[1,3]dioxolane-4-carboxylic acid ethyl ester (Compound No. 42)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.1 (1H, bs, CO_2H), 8.16 (1H, d, N*H*), 6.99 (2H, d, J=7.5Hz) & 6.64 (2H, d, J=7.5Hz), 5.12 (1H, s) & 5.08 (1H, s) [OCH_2O], 4.56 (2H, s, OC*H*×2), 4.15 (1H, m, NC*H*), 4.03 (2H, q, J=3.9Hz, OCH_2), 2.95 (2H, m, CH_2Ar) and 1.22 (3H, t, J=6.9Hz, CH_3).

(S)-2-{[(4R, 5R)-5-(2,6-Dichloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic-acid (Compound No. 45)

^{1}H NMR (DMSO-d_6, 300MHz):δ 10.45 (1H, s, N*H*), 10.13 (1H, s, N*H*), 8.78 (2H, d, J=6Hz), 8.39 (1H, d, N*H*), 7.86 (2H, d, J=6Hz), 7.67 (2H, d, J=6Hz), 7.54 (2H, d, J=6Hz), 7.37 (1H, m) & 7.24 (2H, d, J=9Hz) [aromatic], 5.24 (1H, s) & 5.19 (1H, s), [OCH_2O], 4.69 (1H, d, J=3Hz) & 4.63 (1H, d, J=3Hz) [OC*H*×2], 4.50 (1H, m, NC*H*) and 3.05 (2H, m, CH_2Ar).
LCMS (m/e): 573.4 (M+1, 100%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-isopropylcarbamoyl-[1,3]dioxolane-4-carbonyl}-amino]- propionic acid (Compound No. 47)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.21 (1H, d, NH), 7.99 (1H, d, N*H*), 7.56 (2H, d, J= 7.5 Hz), 7.46 (1H, m), 7.17 (2H, d, J=8.1 Hz) & 6.96 (2H, d, J=8.4 Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.09 (1H, s) & 5.06 (1H, s) [OCH_2O], 4.48 (1H, d, J=3.9 Hz) & 4.35 (1H, d, J=3.9Hz) [OC*H*x2], 4.46 (1H, m, NC*H*) 3.89 (1H, m, NC*H*CH_3), 3.08 (2H, m CH_2Ar) and 1.08 (3H, d, J=6.3 Hz) & 1.07 (3H, d, J=6.3 Hz) [CH_3 x 2].
LCMS (m/e) 525.4 (M+1, 100%).

(S)-2-{[(4R,5R)-5-(Benzothiazol-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic-acid (Compound No. 53)

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.40 (1H, d, NH), 8.00 (1H, d, J=6Hz), 7.78 (1H, d, J=9Hz), 7.53 (2H, d, J=9Hz), 7.45 (2H, m), 7.32 (1H, t, J=6Hz), 7.19 (2H, d, J=9Hz) & 6.95 (2H, d, J=9Hz) [aromatic], 5.25 (1H, s) & 5.12 (1H, s) [OCH_2O], 5.14 (2H, ABq, J=6Hz, OCH_2Ar), 4.81 (1H, d, J= 3Hz) & 4.76 (1H, d, J=3Hz) [OC*H* x2], 4.48 (1H, m, NC*H*) and 3.04 (2H, m, CH_2Ar).

LCMS (m/e) 616.4 (M+1, 100%).

(S)-3-[4-(2,6,-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,3-dihydro-indole-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 62)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.26 (1H, m, N*H*), 7.40-8.25 (4H, m) & 6.90-7.20 (7H,m) [aromatic], 5.18 (2H, s, OCH_2Ar), 5.12 (1H, s) & 5.06 (1H, s) [OCH_2O], 3.90-4.55 (5H, m, OC*H* x 2, NCH and NCH_2) and 2.95-3.20 (4H, m, CH_2Ar x2).

LCMS (m/e): 585.7 (M+1, 80 %).

3-3[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(5-methyl-[1,3,4] thiadiazol-2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 63)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.35 (1H, d, N*H*), 7.54 (2H, d, J=9Hz), 7.46 (1H, m), 7.17 (2H, d, J=9Hz) & 6.95 (2H, d, J=9Hz) [aromatic], 5.10-5.22 (4H, m, OCH_2Ar and OCH_2O), 4.99 (1H, s) & 4.72 (1H, m) [OC*H* x2], 4.50 (1H, m, NC*H*), 3.03 (2H, m, *CH_2Ar)* and 2.63 (3H, s, ArCH_3).

LCMS (m/e): 581.6 (M +1, 100%).

(S)-2{[(4R,5R)-5-(Biphenyl–2-yl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-phenyl-propionic acid (Compound No. 64)

^{1}H NMR (DMS-d_6, 300 MHz):δ 9.32 (1H, s, N*H*), 8.29 (1H, d, N*H*), 7.70 (1H, d, J=7.8Hz) & 7.20-7.45 (12H, m) [aromatic], 4.98 (1H, s) & 4.93 (1H, s) [OCH_2O], 4.48 (1H, m, NC*H*), 4.48 (1H, d, J=3.3Hz) & 4.44 (1H, d, J=3.6Hz) [OC*H*×2] and 3.08 (2H, m, CH_2Ar).

LCMS (m/e): 461.4 (M+1, 100%).

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-2-phenyl-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 98)

^{1}H NMR (DMSO, 300MHz):δ 7.56-7.36 (10H, m), 7.26-7.14 (3H, m), 6.98-6.92 (2H, m), 6.11 (s) & 6.00 (s) [1H], 5.17 (2H, s), 4.96-4.84 (2H, m), 4.25 (1H, m), 3.10-3.01 (2H, m).

LCMS (m/e): 671.02 (M+2, 100%).

(S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(3,4-dimethyl-isoxazol-5-ylcarbamoyl)-[1,3]-dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 107)

^{1}H NMR ($CDCl_3$, 300MHz):δ 10.74 (1H, s), 8.37 (1H, d, 6Hz), 7.54-7.43 (3H, m), 7.18 (2H, d, 9Hz), 6.95 (2H, d, 9Hz), 5.21-5.18 (3H, m), 5.12 (1H,s), 4.66 (1H, s), 4.51-4.43 (1H, m), 3.11-2.94 (2H, m), 2.15 (3H, s), 1.78 (3H, s).

LCMS (m/e): 578 (M^+).

{2-[5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-1,2,3,4-tetrahydro-isoquinolin-3-yl}-3-carboxylic acid (Compound No. 109)

^{1}H NMR (DMSO, 300MHz):δ 9.63 (1H, m), 7.82-7.80 (1H, m), 7.54 (1H, d, 8Hz), 7.37 (1H, m), 7.27-7.20 (5H, bs), 5.41-5.31 (2H, m), 5.21-5.02 (3H,m), 4.77 (1H, m), 4.48 (1H, m), 3.32 (2H, bs), 3.16 (2H, bs).

LCMS (m/e): 431.22 (M+1, 80%), 453.19 (M+Na, 100%).

2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(1H-indol-3-yl)-propionic acid (Compound No. 110)

^{1}H NMR (DMSO, 300MHz):δ 10.85 (1H, s), 8.29-8.20 (1H, m), 7.76 (m) and 7.54-7.51 (m) [2H], 7.32-7.34 (2H,m), 6.98-7.17(3H,m), 5.24-5.04 (2H, m), 4.67-4.74 (2H, m), 4.52-4.54 (1H, bs), 3.24-3.16 (2H, m).

LCMS (m/e): 458 (M+1, 50%).

2-{([4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 111)

^{1}H NMR (DMSO, 300MHz):δ 10.67 (1H, s), 8.38 (1H, m), 7.79 (1H, d, 6Hz), 7.60-7.46 (2H, m), 7.35 (1H, m), 7.19-7.26 (5H, m), 5.26 (1H, s), 5.13 (1H, d, 9Hz), 5.06(1H,s), 4.68-4.73 (1H, m), 4.50-4.55 (2H, m), 3.09-3.00 (2H, m).

LCMS (m/e): 608.17 (M+2, 20%).

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-2-methyl-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 113)

^{1}H NMR (DMSO, 300MHz, D_2O Exchange):δ 7.94 (1H, d, 7.5Hz), 7.68 (1H, m), 7.55-7.16 (6H, m), 6.95-6.97 (3H, d, 8Hz), 5.23 (1H, m), 5.19 (2H, s), 4.70-4.62 (2H, m), 4.51 (1H, m), 3.11 (2H, m), 1.50-1.36 (3H, m).

LCMS (m/e): 607 (M+1, 100%).

(4R,5R)-2,2-Dimethyl-[1,3]dioxolane-4,5-dicarboxylic acid 4-[(2-chloro-phenyl)-amide]-5-({(S)-1-[4-(2,6-dichloro-benzyloxy)-benzyl]-2-methyl-allyl}-amide) (Compound No. 115)

^{1}H NMR ($CDCl_3$, 300MHz):δ 9.06 (1H, s, NH), 8.42 (1H, bs, NH), 7.40-7.05 (9H, m, Aromatic), 6.97 (2H, d, 8.1Hz), 5.23 (2H, s), 4.93 (1H, m), 4.73 (2H, bs), 3.20 (2H, m), 1.55 (3H, s), 1.43 (3H, s).

LCMS (m/e): 621.10 (M+1) [100%], 623 [M+3] [98%] 643.13 $[M+Na]^+$ [10%]

(S)-2-{[(4R,5R)-5-(2-Cyclopentyloxy-5-fluoro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 133)

^{1}H NMR (DMSO-d_6, 300MHz):δ 9.17 (1H, s), 8.375 (1H, d, 9Hz), 7.985 (1H, d, J=9Hz), 7.43-7.54 (3H, m), 7.17-7.19 (2H, m), 7.03-7.05 (1H, m), 6.87-6.96 (3H, m) [10H aromatic and 2NH], 5.09 (1H, s) and 5.20 (1H, s) [O*C*H_2O], 4.87 (1H, bs, OCH(CH_2)2), 4.65-4.67 (2H, m, O*C*H*C*O×2), 4.49 (1H, m, NHC*H*CO), 2.99-3.07 (2H, m, ArC*H*), 1.59-1.86 (8H, m, 4CH_2).

LCMS (m/e): 661.32 (M+1, 100%), 663.3 (M+3, 70%)

3-Benzo[1,3]dioxol-5-yl-3-{[(4R,5R)-5-(2-chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 134)

^{1}H NMR (DMSO-d_6, 300MHz):δ 9.67 (1H, d, J=9Hz), 8.71-8.72 (1H, m), 7.78 (1H, m), 7.51-7.54 (1H, m), 7.26-7.36 (1H, m), 7.24 (1H, m), 6.94-6.97 (1H, m), 6.78-6.83 (2H, m) [7H aromatic+2NH], 5.98 (2H, s, OCH_2O-Ar), 5.09-5.29 (3H, m, O*C*H_2O, NHC*H*Ar), 4.54-4.75 (2H, m, O*C*H*C*O×2), 2.71-2.81 (2H, m, CHCH_2COOH).

LCMS (m/e): 463.23 (M+1, 25%), 485.2 (M+Na, 100%).

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(2'-methoxy-biphenyl-4-yl)-propionic acid (Compound No. 135)

^{1}H NMR (DMSO-d_6, 300MHz):δ 9.66 (1H, s), 8.47 (1H, d, J=9Hz), 7.765 (1H, d, J=9Hz), 7.51-7.54 (1H, d, J=9Hz), 7.21-7.39 (7H, m), 7.00-7.10 (2H, m) [12H aromatic+2NH], 5.26 (1H, s) and 5.13 (1H, s) [OC*H*$_2$O], 4.68-4.72 (2H, m, 2×OC*H*CO), 4.54 (1H, m, NHC*H*CO), 3.74 (3H, s, OCH_3), 3.06-3.18 (2H, m, ArC*H*$_2$).

LCMS (m/e): 525.53 (M+1, 80%), 547.27 (M+Na, 100%).

2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(4-fluoro-phenyl)-propionic acid (Compound No. 136)

^{1}H NMR (DMSO-d_6, 300MHz):δ 9.65 (1H, s, NH), 8.42 (1H, d, 8.1Hz), 7.77 (1H, d, 6.6Hz), 7.53 (1H, dd, 1.2Hz & 6.6Hz), 7.36 (1H, m), 7.26 (3H, m), 7.08 (2H, t, 9Hz), 5.25 (1H, s) & 5.12 (1H, s) [OC*H*$_2$O], 4.70-4.62 (2H, m, 2×OC*H*C(=O)), 4.48 (1H, m, NHC*H*CO), 3.17-3.01 (2H, m, Ar-CH_2).

LCMS (m/e): 437.22 ($M+1^+$, 50%), 459.22 ($M+Na^+$, 100%).

(S)-2-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-(2′,6′-dimethoxy-biphenyl-4-yl)-propionic acid (Compound No. 137)

^{1}H NMR (DMSO, 300MHz):δ 9.65 (1H, bs), 8.49 (1H, d, 9Hz), 7.77 (1H, d, 9Hz), 7.52 (1H, d, 6Hz), 7.35-7.20 (5H, m), 7.11 (2H, d, 6Hz), 6.72 (2H, d, 9Hz), [2H, NH+11H Aromatic], 5.26 (1H, s) & 5.13 (1H, s), (OC*H*$_2$O), 4.70 (2H, s, (2×OC*H*-C(=O)), 4.54 (1H, m, NHC*H*CO), 3.64 (6H, s, 2×O-CH_3), 3.19-3.02 (2H, m, Ar-C*H*$_2$).

LCMS (m/e): 555.29 ($M+1^+$, 100%), 577.29 ($M-Na^+$, 82%).

3-{[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 138)

^{1}H NMR (DMSO, 300MHz):δ 9.61 (1H, bs), 7.80 (1H, t, 6Hz), 7.54 (1H, d, 6Hz), 7.37 (1H, m), 7.25 (1H, m), 5.32-4.96 (4H, m), 3.16 (3H, bs), 2.89 (1H, s).

LCMS (m/e): 343.23 $(M+1)^+$ [65%], 365.16 $(M+Na)^+$ [100%].

3-[[(4R,5R)-5-(2-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-(3,4-dimethoxy-benzyl)-amino]-propionic acid (Compound No. 140)

^{1}H NMR (DMSO, 300MHz):δ 9.60 (1H, d, 3.3Hz), 8.29 (1H, m), 7.78 (1H, bs), 7.52 (1H, bs), 7.26 (1H, bs), 6.91-6.79 (3H, m), 5.31-4.52 (6H, m) (Ar-C*H*$_2$N+OC*H*$_2$O+OC*H*CO×2), 3.73 (6H, s, 2×OC*H*$_3$), 3.67-3.43 (2H, m, NC*H*$_2$), 3.35 (2H, bs, C*H*$_2$COOH).

LCMS (m/e): 151.20 [100%], 493.50 (M+1, 5%] 515.31 [M+Na$^+$, 8%]

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(3,5-dichloropyridin-4-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 142)

^{1}H NMR (DMSO, 300MHz):δ 10.5 (1H, bs), 8.70 (2H, s), 8.39 (1H, d, 9Hz), 7.56-7.45 (3H, m), 7.19 (2H, d, 9Hz), 6.95 (2H, d, 9Hz) [9 Aromatic + 2N*H*], 5.18-5.25 (4H, m, OC*H*$_2$O) and (ArCH$_2$O), 4.73 (1H, d, J=6Hz) and 4.655 (1H, d, J=3Hz) [OC*H*CO×2], 4.43-4.48 (1H, m, NHC*H*CO), 2.98-3.11 (2H, ArC*H*$_2$CH).

LCMS (m/e): 628.24 (M+1, 50%), 630.2 (M+3, 70%).

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(2-fluoro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 143)

^{1}H NMR (DMSO-d$_6$, 300MHz):δ 10.68 (1H, s, COO*H*), 9.90 (1H, s, N*H*), 8.34 (1H, d, 6Hz, N*H*), 7.75 (1H, bs), 7.46-7.60 (5H, m) and 7.21-7.28 (5H, m) [11H Aromatic], 5.22 (1H, s) and 5.14 (1H, s) [OC*H*$_2$O], 4.65-4.72 (2H, m, 2×OC*H*CO), 4.48 (1H, bs, NHC*H*CO), 3.03-3.14 (2H, m, ArCH$_2$).

LCMS (m/e): 590.30 (M+1, 100%), 592.3 (M+3, 70%)

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-({(4R,5R)-5-[2-(1H-indol-3-yl)-ethylcarbamoyl]-[1,3]dioxolane-3-carbonyl}-amino)-propionic acid (Compound No. 144)

^{1}H NMR (DMSO, 300MHz):δ 10.78 (1H, bs), 10.67 (1H, bs), 8.26 (2H, m), 7.61-6.97 (10H, m), 5.08 (2H, s), 4.54-4.44 (3H, m), 3.13-2.70 (6H, m).

LCMS (m/e): 639.4 (M+1)$^+$ [100%], 641.41 (M+3)$^+$ [68%].

(S)-2-[((4R,5R)-5-Cyclohexylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 145)

^{1}H NMR (DMSO, 300MHz):δ 10.65 (1H, bs), 8.29 (1H, bs), 7.56 (5H, m), 7.19 (2H, d, 9Hz), 5.07 (2H, d, 9Hz), 4.49-4.38 (4H, m), 3.10-3.06 (2H, m), 1.6-1.07 (4H, m), 1.2 (6H, m).

LCMS (m/e): 578, 100% (M+1)$^+$.

(S)-2-([(4R,5R)-5-(Cyclohexylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 147)

^{1}H NMR (DMSO, 300MHz):δ 10.67 (1H, bs), 9.32 (1H, bs), 8.25 (1H, m), 7.71-7.69 (1H, m), 7.61-7.31 (14H, m), 7.20 (2H, d, 9Hz), 5.01 (1H,s), 4.94 (1H,s) 4.54-4.47(3H,m), 3.08-3.06(2H,m).

LCMS (m/e): 698, 100%.

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-({(4R,5R)-5-[(thiophen-2-ylmethyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino)-propionic acid (Compound No. 148)

^{1}H NMR (DMSO, 300MHz):δ 10.68 (1H, bs), 8.84 (1H, bs), 8.30 (1H, d, 9Hz), 7.6-7.46 (5H, m), 7.38 (1H, m), 7.21 (2H, d, 9Hz), 6.94 (2H, d, 9Hz), 5.10 (2H, d, 12Hz), 4.54-4.45 (5H, m), 3.12-2.99 (2H, m).

LCMS (m/e): 592, 100-1.

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(thiazol-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 150)

^{1}H NMR (DMSO-d_6, 300MHz):δ 10.67 (1H, s, N*H*), 8.30-8.36 (1H, m), 7.46-7.61 (6H, m), 7.19-7.27 (3H, m) [9H aromatic and 1N*H*), 5.22 (1H, s) and 5.14 (1H, s) [OCH_2O], 4.765 (1H, d, 3Hz), 4.715 (1H, d, 3Hz) [OC*H*CO×2], 4.48-4.50 (1H, m, NHC*H*CO), 3.03-3.09 (2H, m, ArCH_2).

LCMS (m/e): 579.28 (M+1, 100%), 581.29 (M+3, 70%).

(S)-3-[4-(2,6-Dichloro-benzoylamino)-phenyl]-2-{[(4R,5R)-5-(piperidin-1-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 154)

^{1}H NMR (DMSO, 300MHz):δ 10.67 (1H, bs), 9.15 (1H, bs), 7.60-7.49 (5H, m), 7.20 (2H, d, 9Hz), 5.06 (2H, d, 9Hz), 4.45 (2H, m), 4.31 (1H, m), 3.60 (2H, m), 3.05 (2H, m), 2.67 (2H, m), 1.76 (2H, bs), 1.54 (2H, bs), 1.32 (2H, bs).

LCMS (m/e): 601-100%.

Example 4: (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-diethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 90)

Step a: Synthesis of (4R,5R)-5-(2,6-diethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carboxylic acid ethyl ester.

The solution of the compound (4R,5R)-[1,3]dioxolane-4,5-dicarboxylic acid monoethyl ester (1 g) (Formula III) in thionyl chloride (10 ml) was refluxed at 80°C for 1 hour. The excess of thionyl chloride was removed under reduced pressure and the residue thus obtained was taken into xylene (10ml). To it was added 2,6-diethyl aniline (1.56g) and the resulting reaction mixture was heated at 125°C for 6 hours. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was purified by column chromatography using 20% ethyl acetate in hexane as eluent to furnish the title compound (815 mg).

Step b: Synthesis of (4R,5R)-5-(2,6-diethyl-phenylcarbamoyl)-[1,3]-dioxolane-4-carboxylic acid.

To a solution of the compound obtained from step a above (815 mg) in tetrahydrofuran:methanol:water (3:1:1), was added lithium hydroxide monohydrate (106 mg). The reaction mixture was stirred for 3 hours and concentrated under reduced pressure. The residue thus obtained was taken in water (20 ml) and extracted with ethyl acetate. The aqueous layer was acidified and extracted with ethyl acetate (25 ml). The organic layer was concentrated under reduced pressure to furnish the title compound (715 mg).

Step c: Synthesis of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-diethyl-phenylcarbamoyl)-[1,3]-dioxolane-4-carbonyl]-amino}-propionic acid ethyl ester.

To a solution of the compound obtained from step b above (250 mg) in dichloromethane at 0°C, was added trifluoro acetic acid and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was taken in dimethylformamide and cooled to 0°C. To it was added (S)-2-amino-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid ethyl ester (Bioorg. & Med Chem. Letters 12(2002) 1591-1594) N-methylmorpholine (258 mg), hydroxybenzotriazole (115 mg). The reaction mixture was stirred at 0°C for 30 minutes followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (162 mg) and stirred the reaction mixture it room temperature for overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated. The

residue thus obtained was purified by column chromatography using 50% ethyl acetate in hexane as eluent to furnish the title compound (210 mg).

Step d: Synthesis of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-diethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 90)

To a solution of the compound obtained from step c above (429 mg) in tetrahydrofuran:water:methanol (3:1:1, 5ml), was added lithium hydroxide monohydrate (28 mg) and stirred the reaction mixture for 2 hours. The reaction mixture thus obtained was taken in water. The resulting solution was acidified with aqueous sodium bisulphate and extracted with ethyl acetate. The organic layer was concentrated to furnish the title compound (180 mg).

The analogues of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-diethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 90) described below, can be prepared by reaction of appropriate acid with an amine following the same protocol.

(S)-3[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-dichloro-phenyl carbonyl)-[1,3]dioxolane-4- carbonyl]-amino}-propionic acid (Compound No. 72)

^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.14 (1H, s, N*H*), 8.37 (1H, d, N*H*), 7.30-7.60 (6H, m), 7.19 (2H, d, J=9Hz) & 6.96 (2H, d, J=9Hz) [aromatic], 5.24 (1H, s) & 5.18 (3H, s) [OCH_2Ar and OCH_2O], 4.69 (1H, d, J=3Hz) & 4.64 (1H, d, J=3Hz) [OC*H* × 2], 4.47 (1H, m, NC*H*) and 3.07 (2H, m, CH_2Ar).

LCMS (m/e): 629.5 (M+1, 100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2,6-difluoro-phenyl carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 92)

^{1}H NMR (DMSO-d_6, 300MHz):δ 9.81 (1H, s), 8.19 (2H, s), 7.74 (1H, m), 7.40-7.49 (3H, m), 7.14-7.17 (3H, m) and 6.90-7.02 (3H, m) [12H, aromatic+2NH], 5.12-5.20 (4H, m, OCH_2O and ArCH_2O), 4.63-4.69 (2H, m, 2×OC*H*CO), 4.48-4.50 (1H, m, NHC*H*CO), 2.99-3.07 (2H, m, ArCH_2CH).

LCMS (m/e): 595.11 (M+1, 100%), 597.13 (M+3, 70%).

(S)-2-{[(4R,5R)-5-(2,6-Difluoro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 93)

^{1}H NMR (DMSO-d_6, 300MHz):δ 10.43 (1H, s), 9.92 (1H, s), 8.76-8.78 (2H, m), 8.34-8.37 (1H, m), 7.83-7.84 (2H, m), 7.65-7.71 (3H, m), 7.30-7.36 (1H, m), 7.22-7.24 (2H, m) and 7.08 (1H, m) [11H Aromatic+3NH], 5.21 (1H, s) and 5.12 (1H, s) [OC*H*$_2$], 4.68 (1H, d, J=6Hz) and 4.62 (1H, d, J=6H), [2×OC*H*CO], 4.47-4.50 (1H, m, NHC*H*CO), 3.01-3.10 (2H, m, ArC*H*$_2$CH).

LCMS (m/e): 541.2 (M+1, 100%), 542.2 (M+3, 30%).

(S)-2-{[(4R,5R)-5-(2,6-Diethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-{4-[(pyridine-4-carbonyl)-amino]-phenyl}-propionic acid (Compound No. 94)

^{1}H NMR (DMSO-d_6, 300MHz):δ 10.43 (1H, s), 9.60 (1H, s), 8.77 (2H, d, J=6Hz), 8.34-8.36 (1H, d), 7.83-7.84 (2H, m), 7.66-7.68 (2H, m) and 7.08-7.25 (5H, m) [11H aromatic+2NH], 5.23 (1H, s) and 5.17 (1H, s) [OC*H*$_2$O], 4.65 (1H, d, 3Hz) and 4.60 (1H, d, 3Hz) [2×OC*H*CO], 4.49-4.51 (1H, m, NHC*H*CO), 3.01-3.10 (2H, m, ArC*H*$_2$CH), 2.43-2.50 (4H, m, C*H*$_2$CH$_3$), 1.05-1.10 (6H, m, 2×C*H*$_3$).

LCMS (m/e): 561.3 (M+1, 100%).

SCHEME II (PATH A) PROCEDURE

Example 5: (S)-3-{4-(2,6-Dichloro-benzyloxy)-phenyl-2-{[(4R,5R)-5-(4-methyl-piperazine-1-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid salt with trifluoroacetic acid (Compound No. 44)

Step1: Synthesis of (4R,5R)-{1S-tert-butoxycarbonyl-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethyl-carbamoyl}-[1,3]dioxolane-4-carboxylic acid ethyl ester

O-(2,6-dichloro-benzyl)-L-tyrosine-t-butyl ester (430 mg, 1.08 mmol) was added to the compound of Formula III (20.6 mg, 1.08 mmol) in dry dimethylformamide (5 ml) under stirring. The reaction mixture was cooled to 0°C and then N-methylmorpholine (109 mg, 1.08 mmol) and hydroxybenzotriazole (146 mg, 1.08 mmol) were added and the mixture was stirred for 20 minutes. To the mixture was then added 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl) (206 mg, 1.08 mmol) under stirring. Gradually the reaction mixture was allowed to warm to room temperature and stirred

overnight. Water was added and the reaction mixture was extracted with ethyl acetate (3 X 15 ml). The combined organic extracts were washed with water and brine and dried over anhydrous sodium sulphate solution. Evaporation of the solvent under reduced pressure followed by purification of the residue over a silica gel column using 20% ethyl acetate-hexane solvent mixture as an eluent furnished the title compound. Yield = (350 mg, 57%).

^{1}H NMR($CDCl_3$, 300MHz):δ 7.37 (2H, d, J=7.8Hz), 7.24 (1H, m), 7.10 (2H, d, J=7.8Hz) & 6.97 (2H, m) [aromatic], 5.25 (2H, s, COC*H*$_2$Ar), 5.23 (1H, s) & 5.19 (1H, s) [OC*H*$_2$O], 4.81 (1H, d, J=2.4Hz) & 4.66 (1H, d, J=2.4Hz) [OC*H*×2], 4.73 (1H, m, NC*H*), 4.28 (2H, q, J=6.9Hz, OC*H*$_2$), 3.09 (2H, m, C*H*$_2$Ar), 1.43 (9H, s, C*H*$_3$×3) and 1.32 (3H, t, J=6.3Hz, C*H*$_3$).

Step 2: Synthesis of S-(4R,5R)-5-{1S-tert-butoxy-carbamoyl-2-[4-(2,6-di-chloro-benzyloxy)-phenyl]-ethylcarbamoyl]-[1,3]dioxolane-4-carboxylic acid

Lithium hydroxide monohydrate (26 mg, 0.62 mmol) was added to the ethyl ester obtained from Step 1 above (350 mg, 0.62 mmol) in tetrahydrofuran: water: methanol (3:1:1 ml), was added and the reaction mixture was stirred at room temperature for 2 hours. The solvents were evaporated; the residue was taken into water and extracted the organic layer with ethyl acetate. The aqueous layer was then acidified with saturated aqueous sodium bisulphate solution and then extracted with ethyl acetate (3×20 ml). The combined organic extract was washed with brine and dried over sodium sulphate and concentrated to obtain the title compound as a white solid (330 mg).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.33 (1H, d, NH), 7.56 (2H, J=7.5Hz), 7.47 (1H, m), 7.17 (2H, d, J=8.1Hz) & 6.97 (2H, d, J=8.4Hz) [aromatic], 5.19 (2H, s, OC*H*$_2$Ar), 5.14 (1H, s), & 5.08 (1H, s) [OC*H*$_2$O], 4.56 (1H, d, J=3.6Hz) & 4.53 (1H, d, J=3.6Hz) [OC*H*×2], 4.37 (1H, m, NC*H*), 2.98 (2H, m, C*H*$_2$Ar) (d, J=3.6Hz) [OC*H*×2], 4.37 (1H, m, NC*H*), 2.98 (2H, m, C*H*$_2$Ar) and 1.36 (9H, s, C*H*$_3$×3).
LCMS (m/e): 540.5 (M+1, 50%) and 484.5 ((M-$^+$Bu)+2, 100%)

Step 3: Synthesis of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4-methyl-piperazine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid tert-butyl ester

N-methylpiperazine (57 mg, 0.57 mmol), N-methylmorpholine (58 mg, 0.58 mmol) and hydroxybenzotriazole (78 mg, 0.58 mmol) was added to the acid obtained from Step 2 above (310 mg, 0.57 mmol) in dry dimethyl formamide (5 ml) at 0°C. The reaction mixture was stirred for 20 minutes and then 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl) (109 mg, 0.58 mmol) was added, and gradually warmed to room temperature and the reaction mixture stirred overnight. The reaction mixture was quenched with water and the aqueous layer was extracted with ethyl acetate (3×15 ml). The solvent was evaporated off and the crude organic compound thus obtained was purified through column chromatography using 2.5% methanol: dichloromethane solvent mixture as an eluent, which furnished the title compound as light yellow solid. Yield = (229 mg, 65%).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.26 1H, d, N*H*), 7.56 (2H, d, J=7.5Hz), 7.46 (1H, m), 7.16 (2H, d, J=8.1Hz) & 6.97 (2H, d, J=8.1Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.08 (2H, s, OCH_2O), 4.86 (1H, d, J=3.3Hz), 4.71 (1H, d, J=3.3Hz) [OC*H*×2], 4.38 (1H, m, NC*H*), 3.46 (4H, m, NCH_2×2), 2.97 (2H, m, CH_2Ar), 2.27 (4H, m, NCH_2×2), 2.17 (3H, s, N-CH_3) and 1.37 (9H, s, CH_3×3).

Step 4: Synthesis of (S)-3-{4-(2,6-Dichloro-benzyloxy)-phenyl-2-{[(4R,5R)-5-(4-methyl-piperazine-1-carbamoyl)-[1,3]dioxolane-4-cabonyl]-amino}-propionic acid trifluoroacetic acid salt

Trifluoroacetic acid (2.5 ml) was added to the tert-butyl ester (220 mg, 0.35 mmol) in dichloromethane (2.5 ml) and the reaction mixture was stirred at room temperature for 3 hours. The volatiles were removed under reduced pressure and flushed with nitrogen to obtain the title compound as a yellow hygroscopic solid. Yield = (230 mg, 97%).

^{1}H NMR (DMSO-d6, 300 MHz): δ 10.1 (1H, bs, CO_2*H*), 8.22 (1H, d, N*H*), 7.56 (1H, d, J=87.5Hz), 7.55 (1H, s), 7.45 (1H, m), 7.18 (2H, d, J=8.4Hz) & 6.97 (2H, d, H=8.4Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.14 (1H, s) & 5.11 (1H, s) [OCH_2*O*], 5.06 (1H, d, J=3Hz) & 4.77 (1H, d, J=2.4Hz) [OC*H*×2], 4.49 (1H, m, NC*H*CO), 4.44 (2H, m), 3.43 (3H, bs) & 3.07 (5H, m) [NCH_2×4 (ring) and CH_2Ar] and 2.81 (3H, s, ArCH_3).

LCMS (m/e): 566.1 (M+1, freebase, 90%) and 568.1 (M+3), 100%).

Analogs of (S)-3-{4-(2,6-dichloro-benzyloxy)-phenyl-2-{[(4R,5R)-5-(4-methyl-piperazine-1-carbamoyl)-[1,3]dioxolane-4-cabonyl]-amino}-propionic acid trifluoroacetic acid salt (Compound No. 44) which are described below were prepared by reaction of the appropriate amine with the acid obtained by Example 3, Step 2 following the same protocol.

(S)-2-[{(4R,5R)-5-tert-Butyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 48)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.22 (1H, d, N*H*), 7.40-7.60 (4H, m), 7.17 (2H, d, J=8.1 Hz) & 6.96 (2H, d, J= 8.4 Hz) [aromatic], 5.18 (2H, s, OCH_2Ar), 5.1 (1H, s) & 5.04 (1H, s) [OCH_2O], 4.44 (1H, m, NC*H*), 4.44 (1H, d, J=4.2 Hz) & 4.32 (1H, d, J=3.9Hz), 3.03 (2H, m, CH_2Ar) and 1.27 (9H, s, CH_3 x 3).

LCMS (m/e): 539.4 (M+1, 100 %).

(S)-3-[4-(2,6-Dichloro-benzyloxy-phenyl]-2-[{(4R,5R)-5-(3-methyl-butylcarbamoyl)-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 49)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.26 (1H, d, N*H*), 8.17 (1H, t, N*H*), 7.56 (2H, d, J= 7.5 Hz), 7.46 (1H, m), 7.17 (2H, d, J=8.1 Hz) & 6.96(2H, d, J= 8.4 Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.09 (1H, s) & 5.06 (1H, s) [OCH_2O], 4.47 (1H, d, J=3.6 Hz) & 4.37 (1H, d, J=3.9 Hz) [OC*H*x2], 4.43 (1H, m, NC*H*), 2.95-3.20 (4H, m, NCH_2 and CH_2Ar), 1.55 (1H, m, CHCH_3), 1.32 (2H, m, CH_2CH) and 0.85 (6H, d, J=6.6 Hz, CH_3 x 2).

LCMS (m/e): 553.5 (M+1, 100 %).

(S)-3-[4-(2,6,Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(R)-1-phenyl-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 50)

^{1}HNMR(DMSO-d_6, 300 MHz); δ 8.61 (1H, d, N*H*), 8.22 (1H, d, N*H*), 7.40-7.58 (3H, m), 7.30 (4H, m), 7.10-7.25 (3H, m) & 6.93 (2H, m) [aromatic], 5.17(2H, s, OCH_2Ar), 5.14 (1H, s) & 5.09 (1H, s) [OCH_2O], 4.96 (1H, m, NC*H*), 4.40-4.50 (3H, m, OC*H*x2 and NC*H*), 2.90-3.10 (2H, m, CH_2Ar) and 1.39 (3H, d, J=6.9 Hz, CH_3).

LCMS (m/e): 587.4 (M+1, 100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(S)-1-phenyl-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 51)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.65 (1H, d, N*H*), d, NH), 8.27 (1H, d, N*H*), 7.56 2H, d, J= 7.8 Hz), 7.46 (1H, t, J=7.2 Hz), 7.31 (3H, d, J=3Hz), 7.22 (2H, m) & 6.96 (2H, d, J= 7.8 Hz) [aromatic], 5.18 (2H, s, OCH_2Ar), 5.11 (1H, s) & 5.08 (1H, s) [OCH_2O], 4.96 (1H, m, NC*H*), 4.47 (3H, bs, OC*H*x2 and NC*H*), 3.00 (2H, m), CH_2Ar) and 1.39 (3H, d, J= 6.6 Hz).

LCMS (m/e): 587.4 (M+1, 100%).

(S)-1-{(4R,5R)-5-{(S)-1-Carboxy-2-[4-(2,6-dichlorobenzyloxy)-phenyl]-ethyl-carbamoyl}-[1,3]dioxolane-4-carbonyl}-pyrolidine-2-carboxylic acid benzyl ester(Compound No. 52)

^{1}HNMR(DMSO-d_6, 300 MHz) δ: 8.20 (1H, d, N*H*), 5.18 (2H, s, OCH_2Ar), 5.11 (3H, s) & 5.03 (1H, s) [OCH_2Ph and OCH_2O], 4.76 (1H, d, J=3.6 Hz) & 4.66 (1H, d, J=3.6 Hz) [OC*H* x 2], 4.46 (1H, m) & 4.38 (1H, m) [NC*H* x 2], 3.07 (2H, m, CH_2Ar) and 2.20 (1H, m) & 1.89 (3H, m) [CH_2 X 2 (ring)].

LCMS (m/e): 671.3 (M+1, 100%).

(S)-2-[(4R,5R)-{5-Benzyloxy-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 54)

^{1}HNMR(DMSO-Cl_6, 300 MHz) : δ 11.61 (1H, s, N*H*), 8.29 (1H, d, N*H*) 7.30-7.60 (8H, m), 7.16 (2H, m) & 6.96 (2H, d, J=6Hz) [aromatic], 5.18 (2H, s OCH_2Ar), 5.08 (1H, s) & 5.05 (1H, s) [OCH_2O], 4.81 (2H, s, OCH_2Ph), 4.53 (1H, d, J=3Hz) & 4.37 (1H, d, J=3Hz) [OC*H* x 2], 4.44 (1H, m, NC*H*) and 3.05 (2H, m, CH_2Ar).

LCMS (m/e): 589.4 (m+1, 100%).

(S)-2-[((4R,5R)-{5-allyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 56)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.38 (1H, m, NH), 8.27 (1H, d, N*H*) 7.45-7.60 (3H, m), 7.17 (2H, d, J=8.1 Hz) and 6.96 (2H, d, J=8.4Hz)[aromatic], 5.73 (1H, m, olefinic *H*), 5.18 (2H, s, OCH_2Ar), 5.11 (2H, d, J=6 Hz, olefinicCH_2) , 5.06 (s) & 5.03 (s) [OCH_2O], 4.50 (1H, d, J=3.9 Hz) & 4.43 (2H, m) [OC*H* X 2 and NC*H*] 3.57 (2H, bs, NCH_2 and 3.05 (2H, m, CH_2Ar).

LCMS (m/e): 523.6 (M+1, 100%).

1-{(4R,5R)-5-[(S)-1-Carboxy-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl}-pyrolidine–2-carboxylic acid (Compound No.57)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.18 (1H, d, N*H*), 7.40-7.60 (3H, m), 7.32 (1H, d, N*H*), 7.16 (2H, d, J=8.1Hz) & 6.96 (2H, d, J=8.1Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.13 (1H, s) & 5.06 (1H, s) [OCH_2O], 4.74 (1H, d, J=3.3 Hz) & 4.64 (1H, d, J=3.3 Hz) [OC*H* x 2], 4.47 (1H, m, NC*H*), 4.20 (1H, m, NC*H*), 3.07 (2H, m, CH_2Ar), 2.08 (1H, m) & 1.86 (3H, m) [CH_2 x 2 (ring)].
LCMS (m/e); 581.6 (M+1, 100 %).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(tetrahydro-furan-2-yl-methyl-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 58)

^{1}HNMR($CDCl_3$, 300 MHz): δ 7.34 (2H, d, J=9Hz), 7.10-7.27 (5H, m) & 6.94 (2H, d, J=9Hz) [aromatic], 5.22 (2H, s, OCH_2Ar), 5.09 (1H, d, J=6Hz) & 5.07 (1H, d, J= 6Hz) [OCH_2O], 4.86 (1H, m) & 4.62 (1H, m) [OC*H* X 2), 4.48 (1H, m, NC*H*), 4.02 (1H, m, OC*H*), 3.70-3.90 (2H, m, OCH_2), 3.48 (1H, m) & 3.05-3.25 (3H, m) [NCH_2 and CH_2Ar] and 1.85-2.00 (3H, m) & 1.52 (1H, m) [CH_2 x 2 (ring)].
LCMS (m/e): 567.5 (M+1, 85 %) and 569.5 (M+3, 100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[2-(1H-indol-3-yl)-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 59)
^{1}HNMR(DMSO-d_6, 300 MHz): δ 6.9-7.55 (12H, aromatic), 5.17 (2H, s, OCH_2Ar), 5.11 (1H, s) & 5.05 (1H, s) [OCH_2O], 4.13-4.50 (3H, m, OC*H* x 2 and NC*H*), 3.37 (1H, m) & 2.70-3.20 (3H, m) [CH_2Ar and CH_2Het].
LCMs (m/e): 682.7 (M+1, 80 %).

(S)-3-[4-[(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-[(2-thiophen-2-yl-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 60)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.27 (2H, m, N*H*x2), 7.55 (2H, d, J=6Hz), 7.46 (1H,m) 7.31 (1H,d, J= 6Hz), 7.18 (2H,d, J= 6Hz), 6.96 (3H,d, J=6Hz) & 6.87 (1H, s) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.07 (2H, s, OCH_2O), 4.49 (1H, m, NC*H*), 4.49 (1H, d, J=3Hz) & 4.41 (1H, d, J=3Hz) [OC*H*x2], 3.36 (2H, t, NCH_2), 3.08 (m) & 2.98 (t) [4H, CH_2Ar and CH_2Het].

LCMS(m/e): 593.6 (M+1), 100 %).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-[(pyridin-4-ylmethyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No.61)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 9.00 (1H, t, N*H*), 8.78 (2H, d, J=4.5 Hz), 8.30 (1H, d, N*H*), 7.78 (2H, d, J=5.1 Hz), 7.55 (2H, d, J=7.2 Hz), 7.46 (1H, m), 7.17 (2H, d, J=7.8 Hz) & 6.95 (2H, d, J=8.1 Hz) [aromatic], 5.18 (3H, s) & 5.11 (1H, s) [OCH_2Ar and OCH_2O], 4.30-4.60 (5H, m, OC*H* x 2, NC*H* and NCH_2) and 2.98 (2H, m, CH_2Ar).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-(methyl-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No.65)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.23 (1H, d, N*H*), 7.30-7.60 (6H, m), 7.10-7.22 (4H, m) & 6.94 (2H, d, J=8Hz) [aromatic], 5.16 (2H, s, OCH_2Ar), 5.06 (1H, s) & 4.90 (1H, s) [OCH_2O], 4.64 (1H, d, J=4.2Hz) & 4.29 (1H, d, J=3.9Hz), [OC*H* X 2], 4.28 (1H, m, NC*H*), 3.19 (3H, s, N-CH_3) and 2.94 (2H, m, CH_2Ar).
LCMS (m/e): 573.5 (M+1, 100 %).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl)-2-[{4R,5R)-5-[methyl-(1-methyl-piperidine-4-yl)-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound No. 66)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 9.50 (1H, bs, CO_2H), 8.21 (1H, m, N*H*), 7.56 (2H, d, J=9Hz), 7.46 (1H, m), 7.17 (2H, d, J=6Hz) & 6.96 (2H, d, J= 9Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 4.25-5.15 (5H,m, OCH_2O, OC*H* x 2 and NC*H*), 2.70–3.20 (6H,m, NCH_2 x2 and CH_2Ar), 2.51 (DMSO + N-CH_3 X2), 1.70-2.05 (4H, m, CH_{2x}2 (ring)).
LCMS (m/e): 594.6 (M+1, 100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy-phenyl]-2-{[(4R,5R)-5-(2-fluoro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino-propionic acid (Compound No. 67)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 9.89 (1H, s, N*H*), 8.34 (1H, d, N*H*), 7.76 (1H, t), 7.55 (2H, d, J=9Hz), 7.46 (1H, m), 7.15-7.30 (5H, m), & 6.96 (2H, d, J=9Hz) [aromatic], 5.22 (1H, s) & 5.13 (1H, s) [OCH_2O], 5.18 (2H, s, OCH_2Ar), 4.71 (1H, d, J=6Hz) & 4.65 (1H,d, J=3Hz) [OC*H*x2], 4.49 (1H, m, NC*H*) and 3.07 (2H, m, CH_2 Ar).
LCMS (m/e): 577.6 (M+1, 100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-methoxy-phenyl-carbamoyl)-[1,3]dioxolane-4-carbony]-amino}-propionic acid (Compound No. 68)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 9.17 (1H, s, N*H*), 8.37 (1H, d, J= 8.1 Hz), 8.06 (1H, d, N*H*), 7.55 (2H, d, J=7.5 Hz), 7.45 (1H, m), 7.19 (2H, d, J=8.1Hz), 7.09 (2H, m) & 6.92-6.98 (3H, m) [aromatic], 5.25 (1H, s) & 5.11 (1H, s) [OCH_2O], 5.18 (2H, s, OCH_2Ar), 4.71 (1H, d, J=3.6Hz) & 4.66 (1H, m, J=3.9Hz)[OC*H*x2], 4.48 (1H, m, NC*H*), 3.85 (3H, s, OCH_3) and 3.00 (2H, m, CH_2Ar).

LCMS (m/e): 593.6 (M+1, 100%)

(S)-2-{[(4R,5R)-5-(4-Chloro-phenyl-carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No.69)

^{1}HNMR(DMSO-d_6, 300 MHz) δ 10.30 (1H, s, NH), 8.36 (1H, d, N*H*), 7.72 (1H, d, J=9Hz), 7.56 (2H, d, J=6Hz) 7.47 (1H, m), 7.39 (2H, d, J=9Hz), 7.18 (2H, d, J=6Hz) & 6.96 (2H, m) [aromatic], 5.18 (1H, s) & 5.13 (1H, s) [OCH_2O], 5.16 (2H, s, OCH_2Ar), 4.66 (1H, d, J=3Hz) & 4.61 (1H, d, J=3Hz) [OC*H* x 2], 4.48 (1H, m, NC*H*) and 3.06 (2H, m, CH_2Ar)

LCMS (m/e): 595.5 (M+3, 100%)

(S)-2-{[(4R,5R)-5-(3-Chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 70)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 10.33 (1H, s, N*H*), 8.37 (1H, d, N*H*), 7.87 (1H, s), 7.30-7.60 (5H, m), 7.20 (3H, d, J=9Hz) & 6.96 (2H, t, J=9Hz) [aromatic], 5.20 (1H, s) & 5.14 (1H,s) [OCH_2O], 5.17 (2H, s, OC*H* × 2], 4.67 (1H, d, J=3Hz) & 4.61 (1H, d, J=3Hz) [OC*H*×2], 4.48 (1H, m, NC*H*) and 3.06 (2H, m, CH_2Ar)

LCMs (m/e): 593.5 (M+1, 100 %).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-O-tolyl-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-propionic acid (Compound no.73)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 9.59 (1H, s, N*H*), 8.35 (1H, d, N*H*), 7.30-7.60 (4H, m), 7.20 (5H, m) & 6.95 (2H, d, J= 8.4 Hz) [aromatic], 5.23 (1H, s) & 5.14 (1H, s) [OCH_2O], 5.18 (2H, ABq J= 4.5 Hz, OCH_2Ar), 4.64 (2H, d, J= 5.1 Hz, OC*H*x2), 4.48 (1H, m, NC*H*), 3.06 (2H, m, CH_2Ar) and 2.17 (3H, s, ArCH_3)

LCMS (m/e): 573.5 (M+1, 100 %).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-dimethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl]-amino]-propionic acid (Compound No. 74)

^{1}HNMR(DMSO-d_6, 300MHz):δ 8.20 ((1H, d, NH), 7.56 (2H, d, J=7.5Hz), 7.46 (1H, m), 7.16 (2H, d, J=8.4 Hz) & 6.97 (2H, d, J=8.4 Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5..08 (2H, s, OCH_2O), 4.66(1H, d, J=3.6 Hz) & 4.54 (1H, d, J=3.6 (Hz) [OC*H*x2], 4.45 (1H, m, NC*H*), 3.06 (1H, m) 2.92 (1H, m) [CH_2Ar], 2.92 (3H, s) and 2.84 (3H, s) [NCH_3 X 2].
LCMS (m/e): 511.3 (m+1, 100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl)-2-[{(4R,5R)-5-methyl-carbamoyl-[1,3]dioxolane-4-carbonyl]-amino]- propionic acid (Compound No.75)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.26 (1H, d, N*H*), 8.12 (1H, m, N*H*) 7.55 (2H, d, J=7.5 Hz) 7.46 (1H, m), 7.17 (2H, d, J=8.4Hz) & 6.96 (2H, d, J= 8.4 Hz) [aromatic], 5.18 (2H, s, OCH_2Ar], 5.09 & 5.07 (1H, s) & 5.04 & 4.93 (1H, s) [OCH_2O}, 4.30-4.55 (3H, m, OC*H*X2 and NC*H*), 2.90-3.10 (2H, m, CH_2Ar) and 2.63 (s) & 2.61 (s) [3H, CH_3]
LCMS(m/e) : 497.5 (M+1, 100 %).

(S)-3-[4-[(2,6-Dichloro-benzyloxy)-phenyl]-2-[{(4R,5R)-5-methoxy-carbamoyl-[1,3]dioxolane-4-carbonyl}-amino]-propionic-acid (Compound No. 76)

^{1}HNMR(DMSO-d_6, 300 MHz): δ 8.28 (1H,d, N*H*), 7.55 (1H,d,J=7.5 Hz), 7.45 (1H,m), 7.17 (2H,d, J= 8.1 Hz) & 6.96 (2H,d,J=8.1Hz)[aromatic], 5.19 (2H,s, OCH_2Ar), 5.11 (1H,s) & 5.06 (1H,s) [OCH_2O], 4.54 (1H,d,J=3.9Hz) & 4.35 (1H,d, J= 3.9 Hz) [OC*H*X2], 4.45 (1H,m, NC*H*), 3.61 (3H,s, OCH_3) and 3.05 (2H,m, CH_2Ar).
LCMS (m/e): 513.5 (M+1, 100%).

(4R,5R)-5-{(S)-1-tert-Butoxycarbonyl-2-[4-(2,6-dichlorobenzyloxy-phenyl]-ethylcarbonyl]-[1,3]dioxolane-4-carboxylic acid (Compound No.77)

^{1}HNMR (DMSO-d_6, 300 MHz): δ 8.33 (1H, d, N*H*), 7.56 (2H, d, J=7.5 Hz), 7.47 (1H, m), 7.17 (2H,d, J=8.1Hz) & 6.97 (2H, d, J=8.4 Hz) [aromatic], 5.19 (2H, s, OCH_2Ar), 5.14 (1H, s) & 5.08 (1H, s) [OCH_2O], 4.56 (1H, d, J=3.6 Hz) & 4.53 (1H, d, J= 3.6Hz) [OC*H* x 2], 4.37 (1H, m, NC*H*), 2.98 (2H, m, CH_2Ar) and 1.36 (9H, s, CH_3 x 3)

LCMS (m/e): 540.5 (M+1, 50 %) and 484.5 (M-t-bu)+2, 100 %).

(S)-2,3-[4(2,6-Dichloro-benzyloxy)-phenyl]–2-[{(4R,5R)-5-[2-(4-hydroxy-phenyl)-ethyl-carbamoyl]-[1,3]dioxolane-4-carbonyl}-amino]-propionic-acid (Compound No. 78)

^{1}HNMR (DMSO-d_6, 300 MHz): δ 8.26 (1H, d, N*H*), 8.20 (1H, bs, N*H*), 7.54 (2H, m), 7.48 (1H, m), 7.17 (2H, d, J=6.9Hz), 6.97 (4H, bs) & 6.66 (2H, d, J= 6.3 Hz), 5.18 (2H, s, OCH_2Ar), 5.05 (2H, s, OCH_2O), 4.30-4.48 (3H, m, OC*H* x 2 and NC*H*), 3.24 (2H, m, NCH_2), 3.04 (2H, m) CH_2Ar) and 2.63 (2H, m, CH_2Ar).

LCMS (m/e): 603.5 (M+1, 100%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(pyrrolidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 79)

^{1}H NMR (DMSO, 300 MHz, D_2O Exchange): δ 7.51 (2H, d, 8.4Hz), 7.42 (2H, m), 7.12 (2H, d, 8.4Hz), 6.92 (2H, d, 8.4Hz), 5.15 (2H, s), 5.05 (2H, s), 4.60-4.10 (5H, m), 3.42-2.92 (4H, m), 1.74 (4H, bm).

LCMS (m/e): 537.16 $(M+1)^+$ [100%], 539.17 $(M+3)^+$ [68%]

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-((R)-3-hydroxy-pyrrolidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 80)

^{1}H NMR (DMSO, 300 MHz): δ 8.19 (1H, bs), 7.55 (2H, d, 9Hz), 7.46 (1H, d, 9Hz), 7.16 (2H, d, 6Hz), 6.95 (2H, d, 8.1Hz), 5.18 (2H, s), 5.05 (2H, m), 4.68-4.23 (6H, m), 3.54 (2H, m), 3.00 (2H, m), 1.86 (2H, m).

LCMS (m/e): 553.17 (100%) $[M+1]^+$

1-((4R,5R)-5-((S)-1-tert-Butoxycarbonyl-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethylcarbamoyl)-[1,3]dioxolane-4-carbonyl)-pyrrolidine-2-carboxylic acid (Compound No. 81)

^{1}H NMR (DMSO-d6): 7.56-7.47 (3H, m), 7.175 (2H, d, J= 9Hz), 6.975 (2H, d, J = 9Hz), 5.20 (2H, s), 5.06-5.15 (2H, m), 4.67-4.74 (2H, m), 4.41-4.43 (1H, m), 4.25-4.26 (1H, m), 3.57-3.59 (2H, m), 4.25-4.26 (1H, m), 1.82-2.22 (4H, m), 1.34-1.38 (9H, m).

LCMS (m/e): 637.4 (M^+), 639.3 $(M+2)^+$.

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(1-hydroxymethyl-propyl carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 82)

^{1}H NMR (DMSO, 300 MHz):δ 8.25 (1H, bs, NH), 7.74 (1H, bs, NH), 7.55 (2H, d, 7.8Hz), 7.46 (1H, m), 7.17 (2H, d, 8.1Hz), 6.96 (2H, d, 8.4Hz), 5.18 (2H, s), 5.09 (2H, d, J=6Hz), 4.43-4.52 (3H, m), 3.66-3.28 (3H, m), 2.96-3.09 (2H, m), 1.58-1.23 (2H, m), 0.79 (3H, t, 7.2Hz).

LCMS (m/e): 555.18 [(M+1), 100%].

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-ethylcarbamoyl-[1,3]dioxolane - 4-carbonyl)-amino]-propionic acid (Compound No. 83)

^{1}H NMR (DMSO, 300 MHz):δ 8.25-8.16 (2H, m), 7.56-7.46 (3H, m), 7.16 (2H, d, 8.1Hz), 6.96 (2H, d, 8.1Hz), 5.18 (2H, s), 5.07 (2H, m), 4.51-4.44 (2H, m), 4.37 (1H, m), 3.17-2.97 (4H, m), 1.02 (3H, t, 7.2Hz).

LCMS (m/e): 511.09 (M^+, 100%), 513 (M+2, 60%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-prop-2-ynylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 84)

^{1}H NMR (DMSO, 300 MHz):δ 8.65 (1H, m), 8.26 (1H, d, 6.9Hz), 7.57-7.45 (3H, m), 7.15 (2H, m), 6.96 (2H, d, 8.4Hz), 5.19 (2H, s), 5.09 (2H, m), 4.53-4.36 (3H, m), 3.88 (3H, d, 3.0Hz), 3.17-2.97 (3H, m).

LCMS (m/e): 521.17 (M^+, 100%), 523 (M+2, 60%)

Trifluoroacetate salt of (S)-3-[4-(2,6-Dichloro-benzoloxy)-phenyl]-2-{[(4R,5R)-5-(2-morpholin-4-yl-ethylcarbamoyl)-[1,3]-dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 85)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.5 (1H, bs), 8.4 (1H, t, 8.4Hz), 8.28 (1H, d, 8.2Hz), 7.5 (2H, m), 7.4 (1H, m), 7.18 (2H, d, J=8.4Hz), 7.96 (2H, d, J=8.4Hz), 5.74 (2H, s), 5.1 (2H, d, J=11.4Hz), 4.52 (2H, m), 4.4 (1H, bs), 3.66-3.05 (12H, m).

LCMS (m/e): 596.25 $(M+1)^+$ [100%], 598.22 $[M+2]^+$ [70%].

(S)-3-[4-(2,6-Dichloro-benzoloxy)-phenyl]-2-{[(4R,5R)-5-(piperidin-1-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 86)

^{1}H NMR (DMSO, 300 MHz):δ 8.26 (1H, bs, NH), 7.55 (2H, d, 6Hz), 7.46 (1H, m), 7.16 (2H, m), 6.96 (2H, d, 6Hz), 5.19 (2H, s), 5.07 (2H, m), 4.49-4.34 (4H, m), 3.17-2.73 (6H, m), 1.57-1.2 (6H, m).

LCMS (m/e): 566.19 (M+1) [100%].

(S)-3-[4-(2,6-Dichloro-benzoloxy)-phenyl]-2-{[(4R,5R)-5-(piperidin-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 87)

^{1}H NMR (DMSO, 300 MHz):δ 8.20 (1H, bs, NH), 7.55 (2H, d, 7.2Hz), 7.46 (1H, m), 7.16 (2H, d, 8.4Hz), 6.96 (2H, d, 8.4Hz), 5.18 (2H, s), 5.06 (2H, s), 4.81 (1H, d, 3.9Hz), 4.66 (1H, d, 3.6Hz), 4.45 (1H, m), 3.16-2.95 (6H,m), 1.39-1.55 (6H, bm).

LCMS (m/e): 551.17 $(M+1)^+$ [100%], 553.15 $(M+3)^+$ [66%]

(S)-2-{[(4R,5R)-5-(Bicyclo[2.2.1]hept-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 89)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.14 (1H, m), 7.54-7.60 (3H, m), 7.45-7.48 (1H, m), 7.01-7.04 (2H, m) and 6.85-6.87 (2H, m) [aromatic and 2N*H*], 5.16 (2H, s, ArCH_2O), 5.04-5.06 (2H, bs, OCH_2O), 4.42-4.44 (2H, m, OC*H* CO×2), 3.91 (2H, bs, NHC*H*CO and NHC*H* ring), 3.0 (2H, bs, ArCH_2), 2.30 (1H, bs), 2.14 (1H, bs), 1.84 (1H, bs) and 1.02-1.50 (7H, m) [Bicyclic ring).

LCMS (m/e): 577.2 (M+1, 100%)

(S)-3-[4-(2,6-Dichloro-benzoloxy)-phenyl]-2-{[(4R,5R)-5-(2-isopropyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 91)

^{1}H NMR (DMSO, 300 MHz):δ 9.66 (1H, bs, NHO_2COOH), 8.34 (1H, bs, NH), 7.54 (2H, d, 7.5Hz), 7.45 (1H, m), 7.33-7.16 (6H, m), 6.95 (2H, d, 8.4Hz), 5.21-5.14 (4H, m), 4.62 (2H, dd, 4Hz), 4.47 (1H, m), 2.98-3.16 (2H, m), 2.20 (1H, m), 1.11 (6H, d, 6.8Hz).

LCMS (m/e): 601.12 $(M+1)^+$ [100%], 603.11 $(M+3)^+$ [70%]

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-((R)-2-hydroxy-1-phenyl-ethylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 97)

^{1}H NMR (DMSO, 300 MHz):δ 8.45 (1H, d, J=9Hz), 8.24 (1H, d, J=9Hz), 7.55-7.57 (2H, m), 7.44-7.49 (1H, m), 7.15-7.32 (7H, m) and 6.93-6.96 (2H, m) [aromatic+2NH], 5.11-5.19 (4H, m, $ArCH_2O$ and OCH_2O), 4.84-4.87 (1H, m, NHCHCO), 4.44-4.48 (3H, m, 2OCHCO), 3.59-3.62 (3H, m, NHCH(PR)CH_2OH), 2.98-3.08 (2H, m, $ArCH_2CH$).

LCMS (m/e): 603.15 (M+1, 100%), 605.11 (M+3, 70%)

(S)-2-{[(4R,5R)-5-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 99)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.02 (1H, s), 8.3 (1H, d, J=9Hz), 7.56-7.16 (9H, m), 6.96 (2H, d, 9Hz), 6.32 (1H, s, NH), 5.18 (2H, s), 5.10 (2H, d, 6Hz), 4.57-4.44 (3H, m), 2.97-3.06 (2H, m), 2.32 (3H, s), 1.27 (9H, s).

LCMS (m/e): 695.29 $(M+1)^+$ [85%], 697.27 $(M+2)^+$ [60%]

(S)-2-{[(4R,5R)-5-(2-sec-Butyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 100)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.64 (1H, s), 8.33 (1H, d, J=9Hz), 7.54-7.56 (2H, m), 7.43-7.48 (1H, m), 7.17-7.28 (6H, m) and 6.94-6.97 (2H, m) [11H, aromatic + 2N*H*], 5.15-5.22 (4H, m, OCH_2O and ArCH_2O), 4.61-4.66 (2H, m, 2×OC*H*CO), 4.47-4.49 (1H, m, NHC*H*CO), 2.94-3.11 (2H, m, ArCH_2CH), 2.81-2.86 (1H, m, ArC*H*CH_2), 1.47-1.49 (2H, m, ArCHCH_2), 1.12 (3H, d, J=7Hz CHCH_3) and 0.74 (3H, t, J=7Hz, CH_2CH_3).

LCMS (m/e): 615.28 (M+1, 100%), 617.3 (M+2, 70%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-trifluoromethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 102)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.75 (1H, s), 8.34-8.36 (1H, m), 7.43-7.77 (7H, m), 7.185 (2H, d, J=9Hz) and 6.96 (2H, d, J=9Hz) [11H aromatic + 2NH], 5.15-5.20 (4H, m, OCH_2O) and ArCH_2O), 4.685 (1H, d, J=3Hz), 4.635 (1H, d, J=3Hz) [2×OC*H*CO], 4.44-4.48 (1H, m, NHC*H*CO), 2.94-3.10 (2H, m, ArCH_2CH)

LCMS (m/e): 627.2 (M+1, 100%), 629.24 (M+3, 70%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-isopropoxy-phenyl carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 103)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.14 (1H, s), 8.385 (1H, d, 9Hz), 8.11 (2H, d, 6Hz), 7.43-7.56 (3H, m), 7.18-7.21 (2H, m), 7.08-7.09 (2H, m) and 6.93-6.98 (3H, m) [aromatic+2NH], 5.12 (1H, s) and 5.24 (1H, s) [OCH_2O], 5.18 (2H, s, ArCH_2O), 4.59-4.69 (3H, m, 2×OC*H*CO and NHC*H*CO), 4.45-4.50 (1H, m, ArOC*H*), 2.95-3.11 (2H, m, ArCH_2) and 1.28 (6H, d, 6Hz, CH(CH_3)$_2$).

LCMS (m/e): 617.3 (M+1, 100%), 619.2 (M+3, 70%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4-hydroxy-piperidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 104)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.14-8.17 (1H, m), 7.54-7.57 (2H, m), 7.43-7.48 (1H, m), 7.16 (2H, d, 9Hz) and 6.96 (2H, d, J-9Hz), 5.18 (2H, s, ArCH_2O), 5.065 (2H, bs, OCH_2O), 4.82-4.85 (1H, m) and 4.68-4.70 (1H, m), [OCHCO×2], 4.44-4.45 (1H, m NHC*H*CO), 2.97-3.15 (6H, m, 2×NCH_2 and ArCH_2CH), 3.75 (1H, m, OC*H*), 1.70 (4H, m, 2CH_2 ring).

LCMS (m/e): 567.27 (M+1, 100%), 569.26 (M+3, 70%)

(S)-2-[((4R,5R)-5-Cyclopentylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 105)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.22 (1H, d, 8.16Hz), 8.073 (1H, m), 7.57-7.45 (3H, m), 7.16 (2H, d, 8.34Hz), 6.96 (2H, d, 8.4Hz), 5.18 (2H, s), 5.08 (2H, d, 11.4Hz), 4.47-4.46 (2H, m), 4.35 (1H, bs), 4.1 (1H, m), 3.04-2.97 (2H, m), 1.77-1.86 (2H, m), 1.62 (2H, m), 1.48-1.35 (4H, m).

LCMS (m/e): 551.25 (M^+, 100%), 553.27 (M+2, 60%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-hexylcarbamoyl-[1,3] dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 106)

^{1}H NMR (DMSO, 300 MHz):δ 7.56 (2H, m), 7.54-7.57 (1H, m), 7.44-7.49 (2H, d, 6Hz), 6.96 (2H, d, 9Hz), 5.19 (2H, s), 5.07 (2H, d, 9Hz), 4.47-4.48 (2H, m), 4.38 (1H, s), 2.97-3.08 (4H, m), 1.41 (3H, bs), 1.23 (9H, bs), 0.84 (3H, bs).

LCMS (m/e): 567.3 (M^+, 100%), 569.32 (M+2, 70%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(pyridin-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 108)

^{1}H NMR (DMSO, 300 MHz):δ 8.33-8.36 (2H, m), 7.84-8.08 (3H, m), 7.57-7.46 (3H, m), 7.20-6.94 (4H, m), 5.22-5.11 (4H, m), 4.73-4.45 (3H, m), 3.07-3.01 (2H, m).

LCMS (m/e): 560.23 (M^+, 50%), 562.21 (M+2).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(morpholin-4-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 112)

^{1}H NMR (DMSO, 300 MHz):δ 9.34 (1H, s), 8.24 (1H, d, 8Hz), 7.56-7.43 (3H, m), 7.15-7.20 (2H, m), 6.96 (2H, d, 8Hz), 5.18 (2H, s), 5.07 (2H, d, 11Hz), 4.49-4.24 (7H, m), 3.05-2.97 (2H, m), 2.73 (2H, bs).

LCMS (m/e): 568.25 (M^+, 25%), 570.27 (M+2, 20%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4-hydroxy-cyclohexyl carbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 114)

^{1}H NMR (DMSO, 300 MHz):δ 8.22 (1H, d, 8Hz), 7.96 (1H, d, 8Hz), 7.57-7.43 (3H, m), 7.17 (2H, d, 8.8Hz), 6.96 (2H, d, 8.8Hz), 5.18 (2H, s), 5.06 (2H, d, 10Hz), 4.46-4.40 (2H, m), 4.35 (1H, d, 4.8Hz), 3.39 (2H, bs), 3.07-2.92 (2H, m), 1.81-1.67 (4H, m), 1.33-1.15 (4H, m).

LCMS (m/e): 581.32 (M+1, 80%)

(4R,5R)-[1,3]Dioxolane-4,5-dicarboxylic acid 4-({(S)-1-[4-(2,6-dichloro-benzyloxy)-benzyl]-2-methyl-allyl}-amide) 5-heptylamide (Compound No. 116)

^{1}H NMR (DMSO, 300 MHz):δ 8.14-8.25 (2H, m, NH), 7.43-7.56 (3H, m), 7.17 (2H, d, 8.4Hz), 6.96 (2H, d, 8.4), 5.18 (2H, s), 5.07 (2H, d, 8.8Hz), 4.47 (2H, bs),4.36-4.37 (1H, m) 3.16-2.89 (4H, m), 1.23 (10H, bs), 0.84 (3H, bs).

LCMS (m/e): 581.27 $(M+1)^+$ [85%], 583.25 $[M+3]^+$ [62%], 603.25 $(M+Na)^+$ [88%]

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(2-ethyl-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 117)

^{1}H NMR (DMSO, 300 MHz):δ 9.63 (1H, bs), 7.78 (1H, bs), 7.55 (2H, d, 7.5Hz), 7.46 (1H, d, 8.1Hz), 7.37 (1H, bs), 7.2 (4H, m), 7.05 (2H, bs), 6.87 (2H, d, 8.1Hz), 5.12-5.18 (4H,m), 4.68 (1H, bs), 4.59 (1H, bs), 4.0 (1H, bs), 3.03-2.56 (4H, m), 1.11 (3H, t, 7.5Hz).

LCMS (m/e): 587.27 $(M+1)^+$ [58%], 589.30 $(M+3)^+$ [40%], 609.27 $(M+Na)^+$ [30%].

(S)-2-[((4R,5R)-5-(2-Benzyl-5-tertbutyl-2H-pyrazol-3-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 119)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 10.12 (1H, s), 8.32 (1H, d, 9Hz), 7.55 (2H, d, 6Hz), 7.47 (1H, m), 7.28-7.16 (5H, m), 7.09 (2H, d, 6Hz), 6.96 (2H, d, 9Hz), 6.15 (1H, s, NH), 5.18 (4H, bs), 5.07 (2H, m), 4.63-4.46 (3H, m), 2.70-3.06 (2H, m), 1.21 (9H, s).

LCMS (m/e): 695.29 $(M+1)^+$ [80%], 697.27 $(M+2)^+$ [60%].

(S)-2-[((4R,5R)-5-Cycloheptylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 120)

^{1}H NMR (DMSO, 300 MHz):δ 8.22 (1H, bs, NH), 8.02 (1H, bs, NH), 7.56-7.43 (3H, m), 7.17 (2H, d, 8.3Hz), 6.96 (2H, d, 8.4Hz), 5.18 (2H, s), 5.08 (1H, s), 5.05 (1H, s), 4.28-4.46(3H,m), 3.07-2.89 (3H, m), 1.72-1.23 (12H, m).

LCMS (m/e): 579.27 $(M+1)^+$ [35%], 781.27 $(M+3)^+$ [25%], 60% 25 $[M+Na]^+$ [32%]

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(5-ethylsulfanyl-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 121)

^{1}H NMR (DMSO, 300 MHz):δ 8.31 (1H, d, 6Hz, NH), 7.55 (2H, d, 7.2Hz), 7.45 (1H, m), 7.17 (2H, d, 8.1Hz), 6.95 (2H, d, 8.2Hz), 5.16 (3H, bs), 5.11 (1H, s), 4.66-4.71 (2H, m), 4.43 (1H, bs), 3.23-2.99 (4H, m), 1.32 (3H, t, 7.2Hz).

LCMS (m/e): 627.22 (M+1) [50%], 629.20 [40%], 649.20 [M+Na] [18%]

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4,5-dimethyl-thiazol-2-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 123)

^{1}H NMR (DMSO, 300 MHz):δ 8.32 (1H, d, 7.5Hz), 7.55-7.42 (3H, m), 7.17 (2H, d, 7.5Hz), 6.95 (2H, d, 7.6Hz), 5.19-5.10 (4H, m), 4.66 (2H, m), 4.50-4.43 (1H, m), 3.06-2.99 (2H, m), 2.24 (3H, s), 2.15 (3H, s).

LCMS (m/e): 594.24 (M^+, 80%), 596.3 (M+2, 60%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(4-oxo-piperidine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 125)

^{1}H NMR (DMSO, 300 MHz):δ 8.18 (1H, d, 6Hz), 7.56-7.43 (3H, m), 7.17 (2H, d, 9Hz), 6.97 (2H, d, 9Hz), 5.19-5.12 (4H, m), 5.00 (1H, d, 3Hz), 4.78 (1H, d, 3Hz), 4.4 (1H, m), 3.85-3.67 (4H, m), 3.07-2.99 (2H, m), 2.51-2.36 (4H, m).

LCMS (m/e): 565.22 (M^+), 567 (M+2).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-(indan-5-ylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 127)

^{1}H NMR ($CDCl_3$, 300 MHz):δ 8.29 (1H, bs, NH), 7.55-7.45 (5H, m), 7.13-7.19 (3H, m), 6.92 (2H, d, 6Hz), 5.13-5.20 (4H, m), 4.57-4.64 (3H, m), 3.23-2.76 (6H, m), 2.00 (2H, m).

LCMS (m/e): 599.22 $[M+1]^+$ [100%], 601.24 $[M+3]^+$ [68%].

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-{[(4R,5R)-5-phenethylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 128)

^{1}H NMR (DMSO, 300 MHz):δ 8.22 (2H, m), 7.56-7.45 (2H, m), 7.27-7.16 (8H, m), 6.95 (2H, d, 9Hz), 5.19 (2H, s), 5.11 (2H, s), 4.46-4.38 (3H, m), 3.08-2.96 (2H, m), 2.77-2.70 (2H, m).

LCMS (m/e): 587.21 (M^+, 100%), 589.23 (M+2, 70%).

(S)-2-(((4R,5R)-5-[(Benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-[1,3]dioxolane-4-carbonyl)-amino)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 129)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.72 (1H, bs), 8.32 (1H, bs), 7.62-7.48 (3H, m), 7.22 (2H, d, 8.7Hz), 7.00 (2H, d, 8.4Hz), 6.88 (2H, d, 8.1Hz), 6.77 (1H, d, 8.4Hz), 6.01 (2H, s), 5.22 (2H, s), 5.14 (2H, d, 16.5Hz), 4.57-4.45 (3H, m), 4.25 (2H, d, 6Hz), 3.00-3.12 (2H, m).

LCMS (m/e): 617.29 $(M+1)^+$ [25%], 641.25 $(M+Na)^+$ [15%].

(S)-2-(((4R,5R)-5-Butylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 130)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.22 (1H, bs), 8.14 (1H, bs), 7.57-7.43 (3H, m), 7.17 (2H, d, 8.4Hz), 6.96 (2H, d, 8.4Hz), 5.18 (2H, s), 5.07 (2H, d, 12Hz), 4.48-4.37 (3H, m), 3.11-2.95 (4H, m), 1.42-1.23 (4H, m), 0.85 (3H, t, 7.2Hz).

LCMS (m/e): 539.30 $(M+1)^+$ [100%], 541.26 $(M+2)^+$ [70%], 561.30 $(M+Na)^+$ [60%].

(S)-2-([(4R,5R)-5-(4-Acetyl-piperazine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 131)

^{1}H NMR (DMSO, 300 MHz):δ 8.18 (1H, d, 9Hz), 7.56-7.45 (3H, m), 7.17 (2H, d, 9Hz), 6.97 (2H, d, 9Hz), 5.19 (2H, s), 5.09 (2H, s), 4.91 (1H, bs), 4.72-4.75 (2H, m), 3.59-3.32 (8H, m), 3.00-3.07 (2H, m), 2.01 (3H, s).

LCMS (m/e): 594.23 (M^+, 70%), 596.25 (M+2, 50%), 597.26 (M+3)

(S)-2-([(4R,5R)-5-(2-Cyclopentyloxy-phenylcarbamoyl)-[1,3]dioxolane-4-carbonyl]-amino}-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 132)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 9.09 (1H, s), 8.37 (1H, d, J=6Hz), 8.15 (1H, d, J=9Hz), 7.44-7.55 (3H, m), 7.18-7.21 (2H, m), 6.91-7.07 (5H, m) [11 aromatic+2N*H*], 5.11 (1H, s) and 5.22 (1H, s) [OCH_2O], 5.18 (2H, s, ArCH_2O), 4.90-4.93 (1H, m, OCHCH_2), 4.66 (2H, bs, O*CH*CO), 4.50-4.53 (1H, m, NHC*H*CO), 3.00-3.08 (2H, m, ArCH_2), 1.60-1.91 (8H, mCH_2 ring).

LCMS (m/e): 643.4 (M+1, 100%), 645.3 (M+3, 70%)

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5R)-5-phenethylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 139)

^{1}H NMR (DMSO, 300 MHz):δ 8.25 (1H, bs, NH), 8.14 (1H, bs, NH), 7.55 (2H, d, 7.5), 7.46 (1H, m), 7.17 (2H, d, 8.4Hz), 6.96 (2H, d, 8.4Hz), 5.18 (2H, s), 5.08 (1H, s), 5.05 (1H, s), 4.46 (2H, bs), 4.36-4.37 (1H, t, 3.9Hz), 3.17-2.96 (4H, m), 1.23 (12H, bs), 0.84 (3H, t, 6.6Hz).

LCMS (m/e): 595.36 $(M+1)^+$ [54%], 597.33 [38%] $(M+3)^+$, 617.35 $(M+Na)^+$ [30%].

(S)-3-[4-(2,6-Dichloro-benzylamino)-phenyl]-2-{[(4R,5R)-5-(4-methyl-piperazine-1-carbonyl)-[1,3]dioxolane-4-carbonyl]-amino}-propionic acid (Compound No. 152)

^{1}H NMR (DMSO, 300 MHz):δ 10.66 (1H, bs), 8.31 (1H, m), 77.49-7.58 (4H, m), 7.20 (2H, d, 6Hz), 5.10 (2H, d, 9Hz), 4.75 (1H, m), 4.75 (2H, bs), 3 (4H, m), 2.96 (4H, m), 2.50-2.52(2H, m).

LCMS (m/e): 579, 100%

(S)-2-[((4R,5R)-5-Cyclopropylcarbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzoylamino)-phenyl]-propionic acid (Compound No. 153)

^{1}H NMR (DMSO, 300 MHz):δ 10.65 (1H, bs), 8.31 (1H, bs), 8.20 (1H, bs), 7.58-7.46 (5H, m), 7.16 (2H, m), 5.05 (2H, d, 6Hz), 4.52 (1H, m), 4.36 (2H, m), 3.00-3.12 (2H, m), 2.68-2.71 (1H, m), 0.63 (2H, m), 0.50 (2H, m).

LCMS (m/e): 536, 100%.

SCHEME II, PATH C PROCEDURE

Example 6: (4R,5R)-5-{(S)-1-carboxy-2-[4-(2,6-dichlorobenzyloxy)-phenyl]-ethyl carbamoyl}-[1,3]dioxolane-4-carboxylic acid Compound No. 35)

Step a: Synthesis of (4R,5R)-5-[(S)-1-benzyloxycarbonyl-2-(4-hydroxy-phenyl)-ethylcarbamoyl]-[1,3]dioxolane-4-carboxylic acid ethyl ester

To a solution of the compound of Formula III (1 g) in dimethylformamide (10 ml) at 0°C, was added L-tyrosine benzyl ester p-toluene sulphonic acid salt (2.3 g), hydroxybenzotriazole (0.78 g) and N-methylmorpholine (1.3 g). The reaction mixture was stirred for 30 minutes at the same temperature followed by the addition of 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1 g). The reaction mixture was stirred at room temperature for overnight, diluted with ethyl acetate and water. The organic layer was separated and washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 40% ethyl acetate in hexane as eluent to furnish the title compound (1.5 g).

Step b: Synthesis of (4R,5R)-5-{(S)-1-benzyloxy carbonyl-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethylcarbamoyl-[1,3]dioxolane-4-carboxylic acid ethyl ester

To solution of the compound obtained from step a above (500 mg) in acetone (5 ml), was added potassium carbonate (310 mg) and stirred the reaction mixture at room temperature for 10 minutes. To it was added benzyl 2,6-dichlorobenzyl bromide (285 mg) and stirred the reaction mixture at 60-70°C for 8 hours. The reaction mixture was concentrated under reduced pressure. The residue thus obtained was washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 30% ethyl acetate in hexane as eluent to furnish the title compound (1.16 g).

Step c: Synthesis of (4R,5R)-5-{(S)-1-carboxy-2-[4-(2,6-dichlorobenzyloxy)-phenyl]-ethylcarbamoyl}-[1,3]dioxolane-4-carboxylic acid (Compound No. 35)

To a solution of the compound obtained from step b above (150 mg) in tetrahydrofuran: methanol: water (3:1:1) (1 ml) was added lithium hydroxide monohydrate (26 mg). The reaction mixture was stirred for overnight and concentrated under reduced pressure. The residue thus obtained was taken in water and extracted with ethyl acetate. The aqueous layer was acidified using sodium bisulphate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound (100 mg).

^{1}H NMR (DMSO, 300 MHz):δ 8.26 (1H, d, 6Hz), 7.57-7.46 (3H, m), 7.17 (2H, d, 9Hz), 6.96 (2H, d, 9Hz), 5.19 (1H, s), 5.11 (1H, s), 5.05 (1H, s), 4.54-4.43 (3H, m), 3.08-2.97 (2H, m).

LCMS (m/e): 484 (M^+).

SCHEME II, PATH B PROCEDURE

Example 7: (4R,5R)-5-{(S)-1-carboxy-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethyl carbamoyl]-[1,3]dioxolane-4-carboxylic acid ethyl ester (Compound No. 46)

Step a: Synthesis of (4R,5R)-5-{(S)-1-tert-butoxycarbenyl-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethylcarbamoyl}-[1,3]dioxolane-4-carboxylic acid ethyl ester

To a solution of the compound of Formula III (1.32 g) in dimethylformamide (10 ml) at 0°C, was added N-methylmorpholine (703 mg), hydroxybenzotriazole (939 mg) and (S)-2-amino-3-[4-(2,6-dichlorobenzyloxy)-phenyl]-propionic acid tert-butyl ester (2.75 g). The reaction mixture was stirred at same temperature for 30 minutes followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.32 g). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was diluted with ethylacetate and water. The organic layer was separated and washed with water and brine. The combined organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound (2.7 g).

Step b: Synthesis of (4R,5R)-5-{(S)-1-carboxy-2-[4-(2,6-dichloro-benzyloxy)-phenyl)ethylcarbamoyl]-[1,3]dioxolane-4-carboxylic acid ethyl ester (Compound No. 46)

To the solution of the compound obtained from step a above (220 mg) in dichloromethane (2.5 ml), was added trifluoroacetic acid (2.5 ml). The reaction mixture was stirred for 2 hours and concentrated under reduced pressure. The residue thus obtained was taken in water and ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound (165 mg).

^{1}H NMR (DMSO, 300MHz):δ 8.30 (1H, m), 7.55-7.44 (3H, m), 7.15 (2H, d, 6Hz), 6.94 (2H, d, 6Hz), 5.17-5.04 (4H, m), 4.55-4.40 (3H, m), 4.14 (2H, q, 6.9Hz), 3.08-2.94 (2H, m), 1.19 (3H, t, 7.2Hz).
LCMS (m/e): 512 (M^++1).

Example 8: (S) –2-[((4R,5R)-5-Carbamoyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 96)

To the (4R,5R)-5-{(S)-1-carboxy-2-[4-(2,6-dichloro-benzyloxy)-phenyl)ethylcarbamoyl] -[1,3]dioxolane-4-carboxylic acid ethyl ester (250mg) (Compound No. 46)

was added methanolic ammonia (20 ml) and stirred the reaction mixture for 4 days at room temperature. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was taken in ethyl acetate and washed with dilute aqueous hydrochloric acid and water and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish the title compound (230 mg).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.25 (1H, d, J=8Hz), 7.54-7.59 (3H, m), 7.43-7.48 (2H, m), 7.16-7.18 (2H, m) and 6.95-6.97 (2H, m) [7 aromatic+3NH], 5.18 (2H, s, OCH_2Ar), 5.05-5.09 (2H, m, OCH_2O), 4.35-4.49 (3H, m, 2×OC*H*CO and NHC*H*CO), 2.95-3.09 (2H, m, ArCH_2CH).

LCMS (m/e): 483.0 (M+1, 100%), 485 (M+3, 70%).

SCHEME III, PATH A PROCEDURE

Example 9: (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-hydroxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 95)

Step a: Synthesis of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-hydroxy methyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid tert butyl ester

To a solution of compound No. 77 (250 mg) at -15°C in 1,2-dimethoxyethane (2 ml) was added N-methylmorpholine hydrochloride salt (51 mg) and isobutyl chloroformate (70 mg). N-methylmorpholine was removed by filtration, washed with 1,2-dimethoxyethane (10 ml) and the filtrate was cooled to -10°C. To the filtrate was added a solution of sodium borohydride in water (2 ml) followed by the addition of water and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure and the residue thus obtained was purified by column chromatography using 50% ethyl acetate in hexane to furnish the title compound (180 mg).

Step b: Synthesis of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-hydroxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid

To a solution of the compound obtained from step *a* above (150 mg) in dichloromethane (2 ml), was added trifluoroacetic acid (2 ml) and stirred the reaction mixture at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was taken in water and basified using aqueous lithium hydroxide and washed with ethyl acetate. The aqueous layer was acidified and extracted with ethyl acetate. The organic layer was concentrated and the residue thus obtained was

purified by column chromatography using 40% ethyl acetate in hexane as eluent to furnish the title compound (130 mg).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.06-8.09 (1H, m), 7.43-7.57 (2H, m), 7.14-7.17 (3H, m) and 6.95-6.98 (2H, m) [7H aromatic+1NH], 5.18 (2H, bs, ASCH_2O), 5.06 (1H, s) and 4.89 (1H, s) [OCH_2O], 4.46 (1H, m, NHCHCO), 4.04-4.09 (1H, m, OC*H*CO), 3.79 (1H, bs, OC*H*CH_2), 3.58-3.62 (2H, m, CHCH_2OH), 2.92-3.11 (2H, m, ArCH_2CH).
LCMS (m/e): 470.07 (M+1, 100%), 472.05 (M+3, 70%).

SCHEME III, PATH B PROCEDURE

Example 10: (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-methyl-amino]-propionic acid (Compound No. 126)

Step a: Synthesis of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxy methyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid tert butyl ester and (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-methyl-amino]-propionic acid tert-butyl ester

To a solution of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-hydroxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid tert butyl ester (200 mg) in tetrahydrofuran (5 ml) at 0°C was added sodium hydride (14 mg) and stirred the reaction mixture for 30 minutes at same temperature. To it was added methyl iodide (108 mg) and stirred the resulting reaction mixture for 1 hour at 0°C and subsequently at room temperature for overnight. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified through column chromatography using 25% ethyl acetate in hexane as eluent to furnish (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-methyl-amino]-propionic acid tert-butyl ester (98 mg) and 30% ethyl acetate in hexane as eluent to furnish (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid tert butyl ester (33 mg).

Step b: Synthesis of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-methyl-amino]-propionic acid (Compound No. 126)

To a solution of the compound obtained from step a above (33 mg) in dichloromethane (1 ml), was added trifluoro acetic acid (1 ml) and the reaction mixture was stirred for 2 hours. The reaction mixture was concentrated under reduced pressure to furnish the title compound (82 mg).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 7.42-7.56 (3H, m), 7.12-7.21 (2H, m), 7.12-7.21 (2H, m), 6.93-6.98 (2H, m) [Aromatic] 5.18-5.19 (2H, bs, ArC*H*$_2$O), 4.87-5.01 (2H, m, OC*H*$_2$O), 4.51-4.55 (1H, m, OC*H*CO), 4.25-4.4 (1H, m, OC*H*CH$_2$), 3.82-3.83 (1H, m, OCC*H*NH), 3.17-3.33 (6H, OC*H*$_2$CH, NC*H*$_3$ and OC*H*$_3$), 2.76-2.99 (5H, m, NC*H*$_3$ and ArC*H*$_2$).

LCMS (m/e): 498.3 (M+1, 100%), 500.31 (M+3, 70%).

Example 11: (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 141)

Step a: (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 141)

To a solution of the compound 3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-methyl-amino]-propionic acid tert-butyl ester (obtained from step a, Example 10) (98 mg) in dichloromethane (1 ml), was added trifluoroacetic acid (1 ml) and stirred the reaction mixture for 1 hour. The reaction mixture was concentrated to under reduced pressure to furnish the title compound (24 mg).

^{1}H NMR ($CDCl_3$, 300 MHz):δ 7.36-6.96 [8H, m, Aromatic+NH), 5.24 (2H, bs, OC*H*$_2$-Ar), 5.13 (1H, s) & 5.10 (1H, s) [OC*H*$_2$O], 4.86 (1H, m, OC*H*CO), 4.22 (2H, m) (NHC*H*C(=O) & OC*H*CH$_2$), 3.73-3.57 (2H, m, OC*H*$_2$), 3.41 (3H, s, OC*H*$_3$), 3.19-3.10 (2H, m, AR-CH$_2$).

LCMS (m/e): 484.29 (M+1, 44%), 486.27 (M+3, 28%), 506.27 (M+Na, 10%).

The analogues (s) of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methoxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 141) described below, can be prepared by using appropriate alkyl halide in place of methyl iodide, respectively, as applicable in each case

(S)-2-[((4R,5S)-5-Benzyloxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionic acid (Compound No. 101)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.11-8.16 (1H, m), 7.43-7.56 (3H, m), 7.31-7.32 (5H, m), 7.14-7.16 (2H,m) and 6.93-6.96 (2H, m) [12H aromatic+1N*H*], 5.16 (2H, s, ArCH_2O), 5.075-5.094 (1H, s) and 4.91 (1H, s) [OCH_2O], 4.46-4.52 (3H, m, OC*H*CO and ArCH_2OCH_2), 4.08-4.11 (1H, m, NHC*H*O), 3.94 (1H, bs, OC*H*CH_2), 3.33-3.55 (2H, m, CHCH_2O), 2.95-3.10 (2H, m, ArCH_2CH).

LCMS (m/e): 560.23 (M+1, 70%), 582.19 (M+Na, 75%).

SCHEME III, PATH C PROCEDURE

Example 12: Trifluoroacetate salt of (S)-3-[4-(2,6-Dichlorobezyloxy)-phenyl]-2-[((4R,5S)-5-pyrrolidin-1-ylmethyl-[1,3]Dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 146)

Step a: Synthesis of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-methane sulphonyloxymethyl-[1,3]-dioxolane-4-carbonyl amino]-propionic acid tert-butyl ester

To a solution of the compound (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-hydroxymethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid tert-butyl ester (step a, Example 9) (200 mg) in dichloromethane (3 ml) at 0°C, was added methanesulphonyl chloride (43.6 mg, 0.06 ml) and triethylamine (0.051 ml). The resulting reaction mixture was stirred for 30 minutes at same temperature and subsequently at room temperature for 4 hours. The reaction mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over anhydrous sodium sulphate and concentrated to furnish the title compound (310 mg).

Step b: Synthesis of (S)-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-5-pyrrolidin-1-yloxymethyl)-[1,3]-dioxolane-4-carbonyl]-amino}-propionic acid tert-butyl ester.

To a solution of the compound obtained from step a above (200 mg) in tetrahydrofuran (5 ml), was added diisopropylethyl amine (98 mg) and pyrrolidine (27 mg). The resulting reaction mixture was refluxed for 12 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was concentrated to furnish the crude compound which was purified by column chromatography using 5% ethyl acetate in dichloromethane as eluent to furnish the title compound (102 mg).

Step c: Synthesis of triflate salt of 1-((4S,5R)-{(S)-1-Carboxy-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethylcarbomoyl}-[1,3]dioxolane-4-ylmethyl)-pyrrolidinum

To a solution of the compound obtained from step b above (102 mg) in dichloromethane (5 ml), was added triethylamine (2.5 ml) and the reaction mixture was stirred for 2 hours. The reaction mixture was concentrated to under reduced pressure to furnish the title compound (68 mg).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 8.24-8.29 (1H, m, NH), 7.43-7.56 (3H, m), 7.18 (2H, d, 6Hz), 6.975 (2H, d, 9Hz) [aromatic], 5.19 (2H, s, ArCH_2O), 5.19 (1H, s) and 5.00 (1H, s) [OCH_2O], 4.48-4.50 (1, m, NHC*H*CO), 4.25-4.28 (2H, m, NCH_2CH), 3.57 (OC*H*CO), 3.42-3.45 (2H, m, NCH_2), 2.99-3.19 (4H, m, NCH_2 and ArCH_2), 1.89-2.05 (4H, m, CH_2-CH_2).

LCMS (m/e): 523.36 (M+1, 100%), 525.34 (M+3, 70%).

SCHEME IV PROCEDURE

Example 13: (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((S)-2,2-dimethyl-[1,3] dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 122)

Step a: Synthesis of lithium salt (S)-2,2-dmethyl-[1,3]dioxolane-4-carboxylic acid

To a solution of (S)-2,2-dimethyl-[1,3]dioxolane-4-carboxylic acid methyl ester (commercially available) (1 g) in tetrahydrofuran:methanol:water (3:1:1), was added lithium hydroxide monohydrate (262 mg) and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to furnish the title compound (890 mg).

Step b: Synthesis of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((S)-2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid ethyl ester

To a solution of the compound obtained from step a above (890 g) in dimethylformamide (15 ml) at 0°C, was added N-methylmorpholine (1.42 g), and (S)-2-amino-3-[4-(2,6-dichlorobezyloxy)-phenyl]-propionic acid ethyl ester (1,47 g), hydroxybenzotriazole (1g) and (1.47g) of trifluoroacetic acid. The reaction mixture was stirred for 30 minutes at the same temperature. To it was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.42 g). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was diluted with water, extracted with ethylacetate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 40% ethyl acetate in hexane as eluent to furnish the title compound (2.2 g).

Step c: Synthesis of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((S)-2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid ethyl ester (Compound No. 122)

To a solution of the compound (150 mg) obtained form step *b* above in tetrahydrofuran: methanol: water (3:1:1, 2ml) was added lithium hydroxide monohydrate (13 mg) and stirred the reaction mixture for 2 hours. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was taken into water and extracted with ethyl acetate. The aqueous layer was acidified with sodium bisulphate and extracted with ethyl acetate. The combined organic extract was washed with water and brine. The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound (93 mg).

LCMS (m/e): 496.26 (M+1, 20%), 518.25 (M+1, 100%).

^{1}H NMR (DMSO-d_6, 300 MHz):δ 7.45-7.62 (4H, m), 7.13 (2H, d, 9Hz), 6.95 (2H, d, J=9Hz) [7 aromatic+1NH], 5.18 (2H, s, ArCH_2O), 5.065 (2H, bs, OCH_2O), 4.82-4.85 (1H, m) and 4.68-4.70 (1H, m) [OCHCO×2], 4.44-4.45 (1H, m, NHC*H*CO), 2.97-3.15 (6H, m, 2×NCH_2 and ArCH_2CH), 3.75 (1H, m, OC*H*), 1.70 (4H, m, 2CH_2 ring).

LCMS (m/e): 567.27 (M+1, 100%), 569.26 (M+3, 70%).

The analogues of (S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((S)-2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 122), described below, can be prepared by condensing an appropriate acid with an amine, as applicable in each case.

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((R)-2,2-dimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 124)

^{1}H NMR (DMSO, 300 MHz):δ 7.63-7.45 (3H, m), 7.12 (2H, d, 8Hz), 6.97 (2H, d, 8Hz), 5.18 (2H, s), 4.49-4.39 (2H, m), 4.11 (1H, t, 10Hz), 3.80-3,84 (1H, m), 3.08-2.99 (2H, m), 1.33 (3H, s), 1.30 (3H,s).

LCMS (m/e): 468.19 (M^+, 25%), 470.22 (M+2, 17%).

(S)-3-[4-(2,6-Dichloro-benzyloxy)-phenyl]-2-[((4R,5S)-2,2,5-trimethyl-[1,3]dioxolane-4-carbonyl)-amino]-propionic acid (Compound No. 149)

^{1}H NMR (DMSO-d_6, 300 MHz):δ 7.66 (1H, d, 8Hz), 7.42-7.55 (3H, m), 7.14 (2H, d, 9Hz), 6.94 (2H, d, 9Hz) [aromatic], 5.18 (2H, s, ArC*H*$_2$O), 4.52-4.55 (1H, m, OC*H*CO), 3.78-3.81 (1H, m, 9Hz, NHC*H*CO), 3.64-3.67 (1H, m, OC*H*CH$_3$), 2.99-3.12 (2H, m, ArC*H*$_2$), 1.34 (3H, s, C*H*$_3$), 1.22-1.24 (6H, bs, C*H*$_3$CH and C*H*$_3$).

LCMS (m/e): 482.34 (M+1, 100%), 484.33 (M+3, 70%), 504.33 (M+Na, 25%).

SCHEME V PROCEDURE

Example 14: (4R,5R)-[1,3]Dioxolane-4,5-dicarboxylic acid 4-({(S)-1-carbamoyl-2-[4-(2,6-dichloro-benzyloxy)-phenyl]-ethyl}-amino)-5-[(2-chloro-phenyl)-amide] (Compound No. 118)

To a solution of the compound (4R,5R)-5-(2-chloro-phenylcarbamoyl)-[1,3]dioxolane-4-carboxylic acid (200 mg) in tetrahydrofuran (10 ml) cooled to -15°C, was added N-methyl morpholine (0.08 ml) and stirred the reaction mixture 10 minutes. To the resulting reaction mixture was added ethyl chloroformate (0.06 ml) and stirred for 20 minutes. To it was added (S)-2-amino-3-[4-(2,6-dichloro-benzyloxy)-phenyl]-propionamide (199 mg) and p-toluene sulphonic acid (13 mg) at –15 to 20°C and stirred the reaction mixture for overnight after warming it slowly to room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure and the residue thus obtained was purified by column chromatography using 7.5% methanol in dichloromethane as eluent to furnish the title compound (196 mg).

^{1}H NMR (DMSO, 300 MHz):δ 9.64 (1H, bs), 8.07 (1H, bs), 7.78 (1H, m), 7.79-7.16 (8H, m), 6.95 (2H, d, 8.7Hz), 5.23-5.06 (4H, m), 4.66-4.46 (3H, m), 3.09-2.92 (2H, m).

LCMS (m/e): 592.15 $(M+1)^+$ [100%], 594.0 (M+3) [98%], 614.17 $[M+Na]^+$ [72%].

Primary Screening- Cell Adhesion Assay

VCAM-1 (100ng/well) was coated in Maxisorp microtitre modules at 4°C overnight. Non-specific blocking was carried out with 3% BSA for two hours and the wells washed with TBS (50mM) Tris, 0.15M NaCl pH 7.4, 0.1mM $CaCl_2$, 0.1mM $MgCl_2$). U937 cells were suspended in fresh medium and incubated at 37°C for two hours before the assay. Cells were then washed in TBS solution and 180 µl of cell suspension ($1x10^6$ cells/ml in TBS buffer) was added per well in VCAM-1 coated wells. 20 µl of sample solution in 50% DMSO and 50% TBS was then added and the cells were incubated at 37°C for one

hour three to five dilutions of each sample were tested in duplicate in a primary screen, samples are tested at 1, 10 and 100 μm. If activity were present, the compounds were tested at lower (<1μm) concentrates. After incubation, the non-adherent cells were removed by washing with TBS and the numbers of adhered cells were quantified by LDH activity estimation. The percent adhesion was calculated as compared to control. Compounds of this invention tested for activity have shown activities following this assay in the range of from about 100 nM to about 100 μM, for example, from about 100 nM to 10 μM, or from about 100 nM to about 3 μM, or from about 100 nM to about 1 μM.

The compounds disclosed herein for utility for the treatment of asthma and the symptoms of asthma, as well as for the treatment of multiple sclerosis, rheumatoid arthritis, allergic rhinitis, inflammatory bowel disease, and other cell adhesion - associated diseases and conditions and relief from the symptoms thereof.